

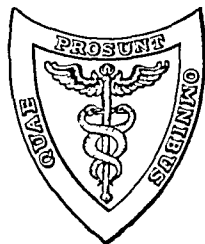
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EDITOR

RICHARD A. KERN, M.D.
ASSISTANT EDITOR

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THE
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ORIGINAL ARTICLES.

CLINICAL OBSERVATIONS ON AORTIC STENOSIS.*

By SYLVESTER MCGINN,

ASSISTANT IN MEDICINE, MASSACHUSETTS GENERAL HOSPITAL,

AND

PAUL D. WHITE,

PHYSICIAN, MASSACHUSETTS GENERAL HOSPITAL; ASSISTANT PROFESSOR OF MEDICINE,
HARVARD MEDICAL SCHOOL, BOSTON.

(From the Cardiographic and Pathologic Laboratories of the Massachusetts General Hospital.)

ALTHOUGH lesions of the aortic valve including "calcareous disease" have been recognized for centuries, little interest has been exhibited in the important clinical condition of aortic stenosis until recently. Over 250 years ago Rayger reported, in 1672, the sudden death of a man whose heart showed an "osseous fusion" of the aortic cusps (quoted by Bonet³ in 1679), and later, in 1706, Cowper⁷ described 3 cases having petrification of the stenosed semilunar valves of the left ventricle. During the next two centuries occasional references, usually brief, were made to the pathology and clinical aspects of aortic stenosis. Finally, to complete the pathologic picture, Mönckeberg,¹² in 1904, described the histology of the aortic cusps and noted atherosclerotic changes at their bases which when present in an extreme degree would produce aortic stenosis.

The etiology of many cases of aortic stenosis has remained in doubt as is illustrated in an extreme degree by 10 patients under 25 years of age reported by Gallavardin,⁹ having the clinical evidence of this lesion but which he thought were neither rheumatic, arteriosclerotic, nor congenital in origin. That aortic stenosis occurs not infrequently in rheumatic heart disease is well known but opinions vary as to the etiology of the calcareous type of the valve lesions. Christian⁵ believed chronic rheumatic endocarditis underlying the process to be highly probable, while Libman discussing Christian's paper expressed the viewpoint that the condition may also be superimposed on congenital

* Presented in brief before the American Clinical and Climatologic Association, Washington, D. C., May 9, 1933.

bicuspid valves, on valves previously affected by subacute bacterial endocarditis, and that it may occur in pure atherosclerosis. Margolis, Ziellessen, and Barnes¹¹ have thought that some cases represent the result of a non-inflammatory degenerative process, and Clawson, Bell, and Hartzell,⁶ following the observations of Mönckeberg, likewise expressed the belief that certain cases have a non-inflammatory origin. Tuohy and Eckman¹⁴ have reported 3 cases with calcareous changes in the aortic valve which, in the absence of a rheumatic history, they thought were best explained by Mönckeberg's theory. Anitschkow¹ has described, in addition to inflammatory valvular changes, an atherosclerosis of the valves with lipid deposits in the middle fibroelastic layers and without cicatricial deformity. In a third group he included those valves with combined inflammatory and atherosclerotic changes in which lipoids replace cicatricial tissue wherever it is found and later undergo calcareous changes resulting in greatly deformed valves.

There are thus certain aspects of aortic stenosis that still require study. These are especially its etiology and frequency, the comparison of those cases showing calcareous change in the aortic valve with those showing no calcareous change, and a comparison of instances of aortic valve stenosis alone with those having associated lesions of the mitral valve. We are presenting herewith statistical data of interest bearing on these points.

Our own material for study has been obtained from a review of 6800 postmortem examinations made at this hospital and from 4800 clinical cardiovascular cases seen in private practice. The criteria in selecting the cases depended in the postmortem series on the statement of the pathologist that the aortic valve was stenosed or on his description indicating that there was a contraction of the valve, and in the clinical series on evidence presented by the patient sufficient to make a definite diagnosis of aortic stenosis.

The requirements stated to be necessary for establishing the clinical diagnosis of aortic stenosis have in the last two generations approached the extremes, with the consequent tendency first to overdiagnose and then later to underdiagnose the condition. The idea of a generation ago that a basal systolic murmur alone permitted the diagnosis of aortic stenosis resulted in the lesion being reported too frequently on clinical examination. The more recent extreme point of view has minimized the frequency of the lesion and may be considered to be overcautious in requiring the following criteria to be present before permitting the diagnosis of aortic stenosis: (1) loud aortic systolic murmur; (2) aortic systolic thrill; (3) absent aortic second sound; (4) plateau or anacrotic pulse; and by some (5) an aortic diastolic murmur. Our experience has indicated that a diagnostic criterion midway between these views is preferable. The diagnosis of aortic stenosis may at times be justified in the presence of a harsh and loud aortic systolic murmur transmitted to the neck, whether or not it be accompanied by one or all of the signs of a confirmatory nature such as an aortic thrill, absent aortic second sound, a plateau pulse, and aortic diastolic murmur; in the presence of evidence of other valvular deformities or of a history of rheumatic infection, and in the absence of evidence of luetic aortitis or of marked hypertension, a loud systolic murmur heard in the second right interspace should strongly suggest stenosis of the aortic valve.

Incidence of Aortic Stenosis. The frequent occurrence of aortic stenosis seems to be confined to certain geographic areas as is indicated by statistical surveys on cardiovascular disease and by personal communications. From the latter and from the data of Davison and Thoroughman⁸ concerning heart disease in the negro race, we may assume that aortic stenosis is a rare condition in the southern section of our country. Norris¹³ found 48 cases of aortic stenosis in a series of 9940 patients (0.4%) showing cardiac lesions at postmortem examinations in two Philadelphia hospitals. The studies of Boas,² Christian,⁵ Clawson,⁶ Margolis,¹¹ and their associates show that aortic valve disease with stenosis is not uncommon in the northern states. Campbell and Shackle⁴ writing in England observed that out of every 6 rheumatic cases 1 had aortic stenosis and insufficiency without mitral stenosis and 1 had aortic stenosis and insufficiency with mitral stenosis. Grant¹⁰ studied 1000 English ex-service men with signs of acquired cardiovascular disease and has recently reported his findings after 10 years of observation. In this group, there were 43 persons who, he believed, had aortic stenosis and regurgitation without mitral stenosis and 6 others who had both aortic stenosis and regurgitation with mitral stenosis.

In our own series of 6800 postmortem cases of all types of disease, there were 123 cases of aortic stenosis (1.8%) and in the clinical group of 4800 cardiovascular patients there were 113 cases (2.3%). There were 37 additional patients in the clinical group who had suggestive but not conclusive signs of aortic stenosis; these questionable cases were not included in this analysis. In the postmortem series, mitral stenosis occurred in 159 cases, coëxisting with aortic stenosis in 50 hearts; and in the clinical series there were 434 cases of mitral stenosis, being associated with aortic stenosis 40 times. The incidence of mitral stenosis in our two groups was 2.3% and 9.2%, as compared to 1.8 and 2.3% for aortic stenosis.

The incidence of aortic stenosis was higher than we had expected since it occurred twice in about every 100 autopsies in the routine postmortem series and in about 3 of every 100 patients with cardiovascular trouble in the clinical series. The relatively close relationship in frequency of mitral stenosis to aortic stenosis was interesting, it being nearly 1 to 1 in the first series and in a ratio of 4 to 1 in the second; moreover, in the postmortem group about every third case of mitral stenosis had a coëxisting aortic stenosis while in the clinical group the ratio was thought to be lower, 1 in every 11 cases. How much of this discrepancy may be due to the more careful routine clinical search for mitral stenosis, which is the rule, than for aortic stenosis, how much to the possibility that the slighter grades of aortic stenosis may produce less clear clinical evidence than the slighter grades of mitral stenosis, and how much to the possibility that the more marked degrees of aortic stenosis are less common than the more marked degrees of mitral stenosis we do not as yet know;

the last mentioned possibility we are investigating further. The discrepancy will undoubtedly be somewhat diminished when aortic stenosis is more zealously searched for, as is indicated by the fact that in the second half of the clinical series twice as many cases were discovered as in the first half of the series. It is of interest to note that the aortic stenosis demonstrated at autopsy was diagnosed clinically in only one-third of the cases. We are as yet much more often missing aortic stenosis when it is present than diagnosing the condition when it is absent.

Etiology of Aortic Stenosis. A definite history of the rheumatic infection was obtained in 23% of the autopsied cases and in 46% of the clinical series; the latter series included another 32% with a questionable rheumatic history. The relative frequency of aortic stenosis in association with mitral stenosis and with a positive rheumatic history in New England is striking.

The presence of important intercurrent infections in the history was noted in about one-third of the postmortem cases and in nearly half of the clinical cases, which incidence probably varies but little from that in the population at large. Those infections most frequently recorded were tonsillitis, pneumonia, influenza, typhoid fever, and gonorrhea in the order named, the majority occurring before the age of 40. It has seemed to us likely that a severe tonsillitis with or without peritonsillar abscess in youth or middle age may be, more than the other infections just named, an etiologic factor in the origin of aortic valve disease found in middle life or old age without mitral valve disease and without a history of rheumatic fever; we have encountered non-syphilitic aortic regurgitation in several such cases developing in males of middle age. Syphilis was not diagnosed in any case of our clinical series and in only 4 cases of our postmortem series; of the postmortem series 54 had had their Wassermann reactions tested and in only 3 were they positive. The diagnosis of subacute bacterial endocarditis was made on 6 occasions in the clinical series but was found only twice in the post-mortem series.

There were 16 cases out of the total 123 autopsied (13%) which should be judged on gross examination to be Mönckeberg's sclerosis of the aortic valve although microscopic sections of the cusps were not available. None of these cases had a positive history of a rheumatic infection. We encountered no cases of congenital aortic stenosis or subaortic stenosis in our postmortem series nor, so far as we can tell, in our clinical series.

The current opinion that aortic stenosis is primarily an affliction of males and that it is consistent with longevity is substantiated by our figures. In the postmortem series 87 (71%) of the 123 cases were males, and 71 (63%) of the 113 clinical cases were of the male sex. In these same series respectively 56 (46%) and 65 (58%) of the patients lived to be 50 or over. The known duration of the

lesion, as well as could be determined for the postmortem cases, was 9.5 years and for the clinical cases 12.7 years up to the present time or until the time of their death.

Symptoms and Signs of Aortic Stenosis. The complaints of the patients were chiefly those of congestive failure, including dyspnea, orthopnea and edema, and were found mostly in the histories of the autopsied patients where the diagnosis of congestive failure had been most frequent. Faintness, dizziness, or actual syncope were also fairly common complaints, having been noted in 22% of the histories of the combined series of 236 cases. Angina pectoris was found in 47 patients (19%) and cardiac asthma in 36 patients (15%).

The clinical diagnosis of aortic insufficiency in our cases of aortic stenosis was made frequently in both series; clinically diagnosable aortic insufficiency was present in 52 of the cases coming to autopsy and in 74 cases of the clinical series. All of our clinical cases of aortic stenosis had loud systolic murmurs at the base of the heart, almost all of which were accompanied by systolic thrills. A basal systolic murmur was recorded in $\frac{1}{2}$ the patients of the postmortem group and a basal systolic thrill in $\frac{1}{4}$; the physical examination very often showed a harsh systolic murmur transmitted all over the precordium, which was frequently attributed antemortem to a mitral lesion. The records contain a few observations as to the wide transmission of the systolic murmurs to neck and back. The aortic second sound was either diminished in comparison with the pulmonary second sound or entirely absent in a majority of the patients, this finding being more common in the autopsied series where the cases of congestive failure were also more numerous. Not rarely, however, the aortic second sound was found to persist even in the presence of well-marked aortic stenosis, later proved at post-mortem examination.

The pulse was described as normal or full in the majority of the patients, a Corrigan pulse being noted in 12 cases of the entire series of postmortem and clinical cases; a plateau pulse was reported in 9.

The systolic blood pressure was found to be 150 mm. of mercury or over in 65 patients (of the total of 236 of both groups) of which 28 were in the postmortem group and 37 were in the clinical group. The blood pressure was above 200 mm. of mercury systolic in 10 patients, of which number 8 belonged to the clinical series. The majority of diastolic pressures varied between 80 and 110 mm. mercury. The average pulse pressure was 60 mm., unexpectedly high.

Auricular fibrillation was diagnosed in 62 of the total of 236 cases, being present most frequently in patients having mitral stenosis also.

Only 10 of the total number of cases failed to show cardiac

enlargement to the left by either percussion or roentgenogram. Infrequently the calcified aortic valves could be seen in fluoroscopic examination and rarely they could be demonstrated by teleroentgenography (7-foot heart films).

Electrocardiograms were taken on 78 patients of the clinical series and on 32 of those of the postmortem series. Left axis deviation was the most common finding, right axis deviation being present in a few cases with mitral stenosis; there was no abnormal axis deviation in others. Various types of delayed conduction were found in 22 of the 110 tracings, there being 6 with full bundle-branch block, 8 with lesser intraventricular block, and 8 with auriculo-ventricular block. Abnormal *T* waves exclusive of the bundle-branch-block cases were seen in 66 of the 110 electrocardiograms.

Of the 172 patients known to be dead out of the total of 236 cases of both series, 12 patients died following operations and 9 others died suddenly; the large majority died in congestive failure. The average duration of the terminal illness was 4.3 months and the average number of attacks of congestive failure was two.

Pathologic Anatomy. The pathologic findings in the 123 cases of the postmortem series indicate the infrequency of syphilis with aortic stenosis, only 2 cases of luetic aortitis having been found and in 1 of these there was also a marked rheumatic endocarditis with mitral stenosis. A microscopic section of an aortic cusp in 1 case contained many easily demonstrable *Treponemata pallida*. A congenitally bicuspid aortic valve was found with the aortic stenosis on 4 occasions, there being only 6 of these congenital lesions recorded in the 6800 autopsies. Subacute bacterial endocarditis was found at autopsy in 2 of the 123 cases, an active endocarditis of other nature in 9, and a chronic rheumatic endocarditis was reported by the pathologist as definite in 18 cases. Additional pathologic data will be given with the comparisons of the various conditions.

A Comparison of Cases of Calcareous and of Non-calcareous Aortic Stenosis (Table 1). Of the 123 cases in the postmortem series, 86 had calcareous changes in the aortic valve, whereas less than half that number (that is, the balance of 37 cases) had aortic stenosis without calcareous changes. The males outnumbered the females in the calcareous group 4 to 1, but the sex distribution was about equal in the smaller non-calcareous group. In relatively few cases did males have aortic stenosis without some evidence of calcareous change. The majority (60%) of the patients with calcareous aortic stenosis were over 50, whereas only 4 of the 37 patients with non-calcareous aortic stenosis were over 50. This indicates that aortic stenosis is consistent with longevity and that aortic valvular calcification is to be expected in aortic stenosis with increasing years. Old age, however, is not the only factor behind the calcareous changes in the cusps, inasmuch as 34 patients (40%) with such changes died before they were 50 years old. This is to be

compared with the finding that 33 (89%) of the 37 cases who showed non-calcareous aortic stenosis died before 50.

TABLE 1.—CASES OF AORTIC STENOSIS IN 6800 AUTOPSIES.

	Calcareous.			Non-calcareous.			Total.
	With a rheumatic history.	Without a rheumatic history.	Total.	With a rheumatic history.	Without a rheumatic history.	Total.	
Number	32	54	86	24	13	37	123
Sex—Male	27	42	69	12	6	18	87
Female	5	12	17	12	7	19	36
Under 50 years of age	17	17	34	24	9	33	67
Over 50 years of age	15	37	52	0	4	4	56
Intercurrent infections	16	25	41	3	3	6	47
Aortic insufficiency (clinical diagnosis)	17	16	33	15	4	19	52
Aortic stenosis (clinical diagnosis)	12	16	28	10	3	13	41
Dyspnea	30	42	72	22	7	29	101
Cardiac asthma	8	11	19	0	0	0	19
Angina pectoris	6	9	15	0	1	1	16
Blood pressures, 150 mm. or over	6	16	22	3	3	6	28
Pulse pressures, average in mm.	53	58	56	73	44	66	59
Auricular fibrillation	12	11	23	13	3	16	39
Wassermann positive, 54 taken	1	1	2	1	0	1	3
Subacute bacterial endocarditis	0	0	0	1	1	2	2
Duration terminal illness (months)	4.2	5.0	4.6	2.5	6.0	3.5	4.3
Heart weight average in gm.	696	572	616	639	467	579	605
Number over 500 gm.	26	37	63	17	7	24	87
Calcareous changes in mitral valve	17	18	35	5	2	7	42
Coronary sclerosis	8	31	39	2	2	4	43
Aortic sclerosis	12	35	47	3	2	5	52
Fusion of cusps into a ring	21	38	59	15	6	21	80
Bicuspid arrangement	6	16	22	3	5	8	30

A rheumatic history was obtained from about $\frac{1}{3}$ of the patients in the calcareous group. It is of interest to note that only 15 of the total of 56 patients of the postmortem series who lived to be over 50 had a clear history of rheumatic infection. The history of intercurrent infections, however, was distinctly more common in these older cases of the calcareous group than in those of the non-calcareous group, the frequency being 47 and 12% respectively. All of 10 cases with a history of gonorrhea and 9 of 12 cases with a history of pneumonia were in the series of cases having calcareous changes. Subacute bacterial endocarditis was present in only 2 of the total postmortem series of 123 cases and both had non-calcareous aortic valve lesions. There were two definite congenital bicuspid aortic valves in each group, calcareous and non-calcareous.

All of the 16 definite cases of Mönckeberg's sclerosis belong, of

course in the calcareous group but the majority of instances of calcareous deposits were found in cases without definite indication of primary Mönckeberg's sclerosis (70 in all), *i. e.*, in the rheumatic cases and in other cases of unknown etiology.

Dyspnea and, to a lesser extent, edema were commonly found in both groups. All of the cases of cardiac asthma were found in the calcareous group as were all of the cases of *angina pectoris* except one. The older age of the calcareous group was undoubtedly of importance in this respect. Syncope and dizziness were complained of equally in both groups. There was practically no difference in the two groups in the known duration of the terminal illness or in the number of attacks of congestive failure suffered by the patients but the calcareous group was known to have had the lesion 1.5 years longer on the average than had the other group.

The clinical diagnosis of aortic stenosis was correctly made in about $\frac{1}{3}$ of each group. Aortic insufficiency was diagnosed clinically in both groups, slightly more often than was aortic stenosis itself, being reported in half of the non-calcareous patients and in 38% of the calcareous. The systolic blood pressure was elevated above 150 mm. mercury more often in the calcareous group; 25% as compared with 16% of the other patients. All of the 8 patients having a diastolic pressure over 110 mm. mercury belonged with the calcareous cases. The pulse pressure was higher than we had expected in both groups with an average of 56 mm. in the calcareous and 66 mm. in the non-calcareous.

The radial arteries were noted to be tortuous, thickened, or sclerotic on 40 occasions, 38 of these being in patients with calcareous aortic valve changes, that is, in the older cases. Auricular fibrillation occurred less frequently in this group (26%) than in the non-calcareous (43%), whereas premature contractions were found about equally in both groups. Among the few instances showing disturbance of conduction by electrocardiogram, bundle-branch block and intraventricular block predominated in the calcareous cases, but only 1 of the 3 cases with auriculoventricular block belonged in that group.

The heart weights were similar in the two groups, averaging 616 gm. in the calcareous group, with 75% above 500 gm., and averaging 579 gm. in the non-calcareous group, with 63% weighing more than 500 gm. Atherosclerotic changes in the aorta and coronary arteries and calcareous involvement of the myocardium and the mitral valve were much more frequent in the older calcareous group. Infarcts of the spleen, lungs, and kidneys occurred in that order and with the same relative frequency in both groups.

Whether or not calcareous changes are present in the aortic valve is relatively unimportant as compared with the condition of aortic stenosis itself, inasmuch as it is the latter which is the factor producing the clinical signs and causing the secondary changes

in the heart. The degree of aortic stenosis may be considerably increased, however, by the deposition of masses of calcium salts and the presence of these may be helpful in establishing the diagnosis of aortic stenosis by fluoroscopic examination or by the 7-foot heart film as a result of the recent improvement of Roentgen ray technique.

A Comparison of Cases with Aortic Stenosis Alone and of Cases with Aortic Stenosis in Association with Other Valve Lesions (Tables 2 and 3). This resolves itself chiefly into a discussion of

TABLE 2.—AORTIC STENOSIS, 4800 CLINICAL CARDIOVASCULAR CASES (15 CASES WITH A NON-STENOTIC LESION OF THE MITRAL VALVE NOT SUMMARIZED).

	Aortic stenosis alone.				Aortic stenosis and mitral stenosis.				Total.
	With a rheumatic history.	Without a rheumatic history.	With a questionable rheumatic history.	Total.	With a rheumatic history.	Without a rheumatic history.	With a questionable rheumatic history.	Total.	
Number	16	23	19	58	29	0	11	40	98
Sex—Males	10	14	12	36	17	0	7	24	60
Females	6	9	7	22	12	0	4	16	38
Age, average in years	50.2	67.8	49.4	56.9	44.4	0	47.2	45.1	52.0
Males, average in years	55.6	69.4	45.5	57.5	46.8	0	47.9	47.2	53.4
Females, average in years	41.3	65.4	56.2	56.0	40.9	0	46.0	42.1	50.0
50 years and over	8	23	11	42	8	0	4	12	54
Aortic insufficiency, clin. diag.	12	6	8	26	29	0	9	38	64
Known duration of lesion in yrs.	14.1	5.4	12.5	10.2	17.8	0	11.1	16.1	13.7
Intercurrent infections	6	6	12	24	17	0	4	21	45
Subacute bact. endocarditis	0	0	1	1	3	0	1	4	5
Dyspnea	12	10	12	34	20	0	7	27	61
Cardiac asthma	2	4	6	12	2	0	2	4	16
Angina pectoris	7	14	4	25	3	0	2	5	30
Edema	2	4	4	10	13	0	3	16	26
Syncope	6	10	5	21	6	0	4	10	31
Well developed and nourished	12	20	16	48	16	0	7	23	71
Auricular fibrillation	1	0	4	5	9	0	5	14	19
Blood pressures, 150 mm. or over	7	14	4	25	7	0	1	8	33
Pulse pressures, average in mm.	63	80	42	61	67	0	49	62	62
With cardiac enlargement	16	23	19	58	28	0	11	39	97
Electrocardiograms L. A. D.*	7	12	8	27	8	0	5	13	40
Bundle branch block	1	0	0	1	1	0	1	2	3
A-V block	1	1	0	2	1	0	0	1	3
Intraventricular block	2	1	0	3	1	0	0	1	4
Number of electrocardiograms	13	18	12	43	17	0	9	26	69

* L. A. D. = Abnormal degree of left axis deviation.

aortic stenosis with and without mitral stenosis. A third group of cases having aortic stenosis in combination with a non-stenosing mitral valve lesion is so closely aligned to the solitary aortic lesion in most respects that these two groups may be considered practically as one. This third group is composed of those cases having slight fibrosis or thickening of the mitral valve and also of those cases in which there are calcareous changes in the mitral leaflets without stenosis of the valve.

Of the 123 autopsied cases of aortic stenosis, there were 50 in which mitral stenosis coëxisted. As has been previously stated with

regard to the total number of autopsies every third case of mitral stenosis had an associated aortic stenosis. There were 36 females in the entire postmortem series of aortic stenosis and 21 of these were in the group having combined lesions of mitral stenosis and aortic stenosis. The majority of the 67 patients dying before the age of 50 showed stenosis of both valves, the mortality before that age for the individual groups being 78% for the combined lesions and 38% for the aortic stenosis alone.

TABLE 3.—CASES OF AORTIC STENOSIS ALONE AND IN ASSOCIATION WITH OTHER VALVE LESIONS (POSTMORTEM SERIES).

	Aortic stenosis alone.			Aortic stenosis and mitral stenosis.			Aortic stenosis and a non-stenotic mitral lesion.			Total.
	With a rheumatic history.	Without a rheumatic history.	Total.	With a rheumatic history.	Without a rheumatic history.	Total.	With a rheumatic history.	Without a rheumatic history.	Total.	
Number	9	26	35	37	13	50	10	28	38	123
Sex—Male	8	20	28	21	8	29	10	20	30	87
Female	1	6	7	16	5	21	0	8	8	36
Under 50 years of age	7	12	19	29	10	39	5	4	9	67
Over 50 years of age	2	14	16	8	3	11	5	24	29	56
Intercurrent infections	3	6	9	6	6	12	7	7	14	35
Aortic insufficiency, clin. diag.	3	11	14	23	4	27	6	5	11	52
Aortic stenosis, clin. diag.	2	10	12	17	2	19	3	7	10	41
Dyspnea	6	17	23	36	12	48	10	20	30	101
Cardiac asthma	1	2	3	4	1	5	3	8	11	19
Angina pectoris	3	7	10	2	0	2	1	3	4	16
Edema	8	15	23	31	9	40	9	17	26	89
Blood pressures, 150 mm. or over	2	8	10	4	2	6	3	9	12	28
Pulse pressures, average in mm.	85	57	63	66	32	59	52	62	60	61
Auricular fibrillation	0	5	5	24	2	26	1	7	8	39
Wassermann positive, 54 taken	1	1	2	1	0	1	0	0	0	3
Subacute bacterial endocarditis	1	0	1	0	0	0	0	1	1	2
Duration terminal illness (months)	3.2	5.0	4.5	3.6	6.8	4.3	3.0	4.0	3.6	4.3
Heart weight average in gm.	627	582	593	622	567	592	883	541	631	605
Number over 500 gm.	6	17	23	27	9	36	10	18	28	87
Calcareous changes in mitral valve	0	0	0	16	7	23	6	13	19	42
Coronary sclerosis	3	11	14	6	3	9	1	19	20	43
Aortic sclerosis	3	15	18	8	3	11	4	19	23	52
Fusion of cusps into a ring	2	13	15	29	11	40	5	20	25	80
Bicuspid arrangement	6	11	17	3	1	4	0	9	9	30

Most of the patients (74%) having mitral and aortic stenosis together had a positive rheumatic history as compared with 26% in the group with aortic stenosis alone. Excepting for tonsillitis the patients having aortic stenosis and mitral stenosis were relatively free from other intercurrent infections such as gonorrhea, influenza and pneumonia.

The symptoms and signs of congestive failure, namely orthopnea, dyspnea and edema, were nearly the same in incidence in both groups, but the frequency of cardiac asthma, angina pectoris, dizziness, and syncope was greater in the patients having aortic stenosis alone. The known length of time that the patient had

aortic valve involvement was less than the average for the entire series when mitral stenosis coëxisted with the aortic stenosis; this same group with combined valve lesions tended to have more attacks of congestive failure.

The clinical diagnosis of aortic stenosis was made correctly in the same proportion in both groups of the postmortem series. In that series aortic insufficiency was noted clinically in 54% of the patients having both aortic and mitral stenosis; this number represents more than half of the total cases with aortic regurgitation in the postmortem series. The difference in the systolic blood pressures of the two groups was not striking; it was found to be over 150 mm. in 48% of the patients with mitral and aortic stenosis as compared with 61% of those with aortic stenosis alone. The average pulse pressures were similar in the two groups. There was a distinct difference in the frequency of auricular fibrillation, which occurred in only 17% of the cases with aortic stenosis alone and in 52% of the group with both aortic and mitral stenosis.

The average heart weights were approximately the same in both groups, with a like number in each weighing more than 500 gm. Sclerosis of the coronary arteries and of the aorta was more common in the group with aortic stenosis alone. There were 42 cases in which calcification was found in the mitral valve; 23 of this number were included in the cases with both aortic and mitral stenosis.

It was found that 24 of the group of 50 cases showing both aortic and mitral stenosis also had calcareous changes in the aortic valve. Two aortic cusps were found to be fused, giving a bicuspid arrangement of the valve on 30 occasions in the whole postmortem series; only 4 of these had an associated mitral stenosis.

Cases with Varying Degrees of Aortic Stenosis. Believing that the degree of stenosis of the aortic valve would be an important factor in determining the clinical signs and the pathologic changes, we have compared three groups of cases having aortic stenosis of varying amount. There are 15 cases in each of the three groups, all of which had calcareous aortic stenosis demonstrated at the postmortem examination and which did not have mitral stenosis. The first group of cases had marked aortic stenosis with calcification but without clinical evidence of insufficiency. Although aortic regurgitation undoubtedly was present to some extent, it was not sufficient to give the usual auscultatory findings. The second group includes those cases of moderate aortic stenosis caused by calcareous deposits at the base of the cusps, which were not accompanied by clinical aortic insufficiency. In the third series of 15 cases, in addition to considerable aortic stenosis all had the clinical signs of aortic insufficiency or the lesion was such that the pathologist thought that it necessarily was present in at least moderate degree.

In the second group, which had only moderate stenosis of the

aortic valve, not 1 case had the discharge diagnosis of aortic stenosis made clinically. This does not indicate, however, that signs and symptoms were not produced by these changes, inasmuch as at least 8 of the 15 cases had records of systolic murmurs heard at the base of the heart, accompanied in 1 case by a thrill. Despite this available evidence attention was not directed toward stenosis of the aortic valve. Congestive failure, as shown by the history of dyspnea and the finding of edema, was very infrequent in this group, edema occurring but once. The aortic second sound was louder than the pulmonary second sound in a greater number of patients of this group than in the other two groups.

TABLE 4.—CASES OF AORTIC STENOSIS OF VARYING DEGREES IN THE POSTMORTEM SERIES.

	Marked calcareous aortic stenosis without clinical insufficiency.	Moderate aortic stenosis with calcareous deposits chiefly at base of cusps without clinical insufficiency.	Calcareous aortic stenosis with marked clinical or pathologic insufficiency.
Number	15	15	15
Sex—Male	11	11	14
Female	4	4	1
Under 50 years of age	2	2	7
Over 50 years of age	13	13	8
Rheumatic fever history	3	1	4
Intercurrent infections	7	7	8
Aortic stenosis, clinical diagnosis	3	0	12
Dyspnea	14	5	15
Cardiac asthma	3	2	3
Angina pectoris	5	3	7
Edema	11	1	14
Blood pressures, 150 mm. or over	6	9	3
Pulse pressures, average in mm.	42	81	52
Auricular fibrillation	1	3	2
Duration terminal illness (months)	4.6	5.8	3.5
Heart weight, average in gm.	588	450	683
Number over 500 gm.	10	5	13
Calcareous changes in mitral valve	7	5	2
Coronary sclerosis	9	10	10
Aortic sclerosis	13	12	11
Fusion of cusps into ring	8	2	10
Bicuspid arrangement	7	2	5

The sex distribution was approximately the same for all three groups, with the males predominating 3 to 1. Of the 15 patients having free aortic insufficiency (Group 3), 7 died before the age of 50 as compared with 2 dying before this age in each of the other two groups. Moreover, the average duration of the terminal illness was slightly shorter for this group than for the other two, and the incidence of angina pectoris was greater. These findings indicate that the presence of free aortic insufficiency with aortic stenosis adds a greater burden on the heart and makes the prognosis less favorable.

The systolic blood pressures were found to be over 150 mm. mercury more frequently in the second group, namely that with

only moderate stenosis, while the third group, that with marked aortic regurgitation, had the fewest pressures above 150 mm. mercury. The average pulse pressure of the patients of the second group, with calcareous changes at the base of the cusps, was 81 mm., of those with aortic insufficiency 52 mm., and of those with marked aortic stenosis but without much aortic insufficiency 42 mm.

The pathologic observations indicate that those hearts in which aortic stenosis was complicated by enough insufficiency to reveal itself clinically were the largest, weighing an average of 683 gm. This compares with the average weights of 588 gm. for the group having marked stenosis and of 450 gm. for the hearts with moderate stenosis. The frequency of sclerosis of the aorta and coronary arteries was equivalent in all three groups. Involvement of the mitral valve by extension of the calcareous process downward from the aortic valve was seen in only 2 cases having marked aortic insufficiency. With the slighter extent of the calcification and deformity of the aortic valve in the group having moderate stenosis only 4 cases were found with the cusps fused into a ring or having a bicuspid arrangement.

Summary and Conclusions. 1. A study of aortic stenosis is presented herewith, based on 123 cases proved at postmortem examination among 6800 necropsies of patients with all types of disease at the Massachusetts General Hospital and 113 clinical cases among 4800 patients studied by us in cardiovascular consultation practice. In the postmortem series 71% of the patients were males and in the clinical series 63%.

2. Aortic stenosis occurred in the postmortem series almost as often as did mitral stenosis. The lower incidence in our clinical series may be due in part to the fact that it is difficult or impossible clinically to diagnose aortic stenosis if the stenosis is but slight in degree. Closer search for the lesion resulted in our finding clinically twice as many cases of aortic stenosis, definite or questionable, in the second half of the clinical series as in the first half. It appears justifiable to make the clinical diagnosis of aortic stenosis when a loud harsh systolic murmur is heard in the region of the second right intercostal space and is transmitted to the neck, in the absence of pronounced aortic dilatation due to luetic aortitis or marked hypertension, especially when there is evidence of other valvular deformity or a history of rheumatic infection. An aortic systolic thrill, a diminished or absent second aortic sound, a plateau pulse, and an aortic diastolic murmur are important confirmatory findings, but it is not necessary to await the presence of all of these signs before making the diagnosis; if we do await all these signs we shall miss a large majority of cases of aortic stenosis often of considerable clinical importance.

3. A comparison has been made, in the postmortem series, of cases showing calcareous changes in the stenosed aortic valve with

cases showing no calcareous change in the valve. Calcareous valvular changes were found more frequently than non-calcareous (86 to 37), with males predominating and living past middle life in the calcareous group while the sexes were evenly distributed in the non-calcareous group, few of whom lived longer than 50 years. Angina pectoris, cardiac asthma, and higher blood pressures were more frequently found in the calcareous group while a positive rheumatic history and auricular fibrillation were more frequent in the non-calcareous group. The average pulse pressures were approximately the same. The heart weights were similar in the two groups but calcareous changes in the mitral valve, aorta, and coronary arteries were much more common, as would be expected, in the older, calcareous group. The presence or absence of calcareous changes in the aortic cusps is clinically relatively unimportant as compared to the aortic stenosis itself, excepting as it alters the degree of stenosis or aids in the Roentgen ray diagnosis.

4. A comparison of the autopsied cases having aortic stenosis alone with those having aortic stenosis combined with mitral stenosis showed males to be represented equally in both groups; females, however, were three times more frequent in the combined than in the isolated group. Mitral stenosis was found much more often in the cases dying under 50, while aortic stenosis alone occurred most commonly in people beyond that age. Angina pectoris was found more often in patients with aortic stenosis alone (14 to 2), while auricular fibrillation occurred much more often in cases with complicating mitral stenosis (26 to 13). The average heart weights were approximately the same for the two groups (612 gm. and 592 gm.). Coronary sclerosis and aortic sclerosis were more common in cases of aortic stenosis alone; sclerotic changes in the mitral valve were found in 23 of the 50 cases with complicating mitral stenosis.

5. In three groups of patients of the postmortem series having various degrees of calcareous aortic stenosis, it was found that the correct diagnosis had not been made clinically in any having only moderate calcareous changes, mostly at the base of the aortic cusps, and that the symptoms of congestive failure were less frequent in this group than in those instances where the lesion was more marked. At least a few of the cases showing only moderate aortic stenosis should have been diagnosed correctly antemortem if proper attention had been directed to the signs that were present. The patients with pronounced aortic insufficiency in addition to aortic stenosis had a shorter terminal illness and died at a younger age than did the cases where stenosis of the valve predominated. The average weight of the hearts in the group with pronounced aortic insufficiency was also higher, the smallest hearts being found in those cases with little or no aortic insufficiency and with only a moderate amount of stenosis.

6. It is evident from this analysis that all grades of aortic stenosis exist, much as in the case of mitral stenosis; that aortic stenosis

even of considerable degree is common, particularly in males; that it is doubtless often caused by infection, especially rheumatism; that calcareous changes are found chiefly in the older patients, no matter what the cause; that aortic stenosis is less serious than aortic regurgitation of high degree, being found in many old patients after years of valvular disease;* that it is sometimes associated with considerable hypertension; that, as in the case of mitral stenosis, the symptoms and signs vary in number and degree with the extent of the aortic stenosis; that aortic stenosis is often overlooked when it should be clinically diagnosed; and that it is an important lesion to search for, even in the lesser grades, because of the progression of the lesion and of the frequency with which it is associated with congestive heart failure.

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INTRAVENOUS INJECTION OF METHYLENE BLUE IN MAN WITH REFERENCE TO ITS TOXIC SYMPTOMS AND EFFECT ON THE ELECTROCARDIOGRAM.

BY J. ERNEST NADLER, M.D.,

ASSISTANT IN MEDICINE, UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE,
NEW YORK UNIVERSITY, CLINICAL ASSISTANT VISITING PHYSICIAN, BELLEVUE
HOSPITAL,

HENRY GREEN, B.S.,

AND

ARTHUR ROSENBAUM, B.S.,

NEW YORK.

(From the Therapeutics Laboratory, University and Bellevue Hospital Medical College, New York University.)

CONSIDERABLE attention has been recently aroused concerning the intravenous injection of methylene blue. At the moment, the

* It is of interest that a few years ago when we searched our records for long-lived patients with heart disease one of the lesions which we failed to find persisting from youth to old age was aortic regurgitation of high degree.

greatest interest centers about its clinical use in the treatment of cyanide,¹ and carbon monoxide poisoning.^{1d, 1e, 1f, 1g, 1i, 1j, 2} In these conditions, however, no altogether acceptable proof has been furnished of its value.³ Its use has also been suggested in cases of methemoglobinemia.⁴

Standard textbooks on the physiologic action of drugs give practically no definite information concerning the action of methylene blue in the body. Although Marshall,⁵ working with malaria, found that as much as 400 gr. (26 gm.) may be given by mouth over several weeks without any toxic symptoms, it has been generally observed that large doses may produce gastric irritation and painful micturition. No mention can be found in the literature of any harmful or untoward effects from intravenous use of this dye; in fact one is led to believe that no more care than usually attends an intravenous injection of saline need be taken. This may be accounted for when it is realized that the patients are usually in coma and on the verge of death at the time the drug is administered. In view of the fact that no study has been made of the effect of intravenous injection of methylene blue in normal man, and that it is both desirable and necessary in order to better understand its action in pathologic conditions, we undertook its investigation.

Material and Method. Eighteen normal adults, who volunteered for this study, were given 50 cc. of a 1% solution of methylene blue intravenously, average therapeutic dose recommended.^{1h} One per cent solution of Methylthionine chlorid, U. S. P. was made by dissolving 1 gm. of the drug⁶ in 100 cc. of hot physiologic saline. It was stirred with a glass rod, filtered, sterilized, and stored in a dark closet for 24 hrs. before using. No attempt was made to dry the salt. The inevitable presence of very small percentages of reductant methylene white⁷ was disregarded.

The speed of the intravenous injection varied in different cases from 5 to 30 min. usually about 10 min. for 50 cc. Two individuals received 3 injections and 3 received 2 injections of the drug. As we found that it took from 3 to 5 days for the dye to be eliminated, a second injection was not given until the dye of the previous injection was no longer present in the body. All subjects had electrocardiograms taken before, during and for some time after the injection of methylene blue, in 1 case Leads I and III were taken simultaneously.

In 6 cases the hemoglobin and methemoglobin values of the blood were ascertained by the method of van Slyke and Hiller.⁸ The only variation from their technique was that the CO was drawn directly from the storage bottle into the mixing chamber of the van Slyke manometric apparatus through a thick-walled capillary pipette fitted with a stopcock and a rubber tip instead of using a Hempel pipette. In collecting the samples of blood, special care was taken to prevent contamination with methylene blue.

Effects. No report of the electrocardiographic changes following the injection of methylene blue in man could be found in the literature. Schott⁹ injected methylene blue intravenously in dogs and failed to find any striking or permanent changes. He obtained a decrease in the *R* wave, while the *T* wave was increased in ampli-

tude. In man we found that the effect on the *T* wave was just the opposite (Fig. 1). In every instance the *T* wave showed a great reduction in height, frequently became isoelectric and occasionally even negative. The *R* wave also usually showed a decrease in height. Recovery was usually complete within 2 hr. after the injection.

The point of action is apparently not vagal, as found by Cook¹⁰ in isolated heart preparations, for no marked change in heart rate

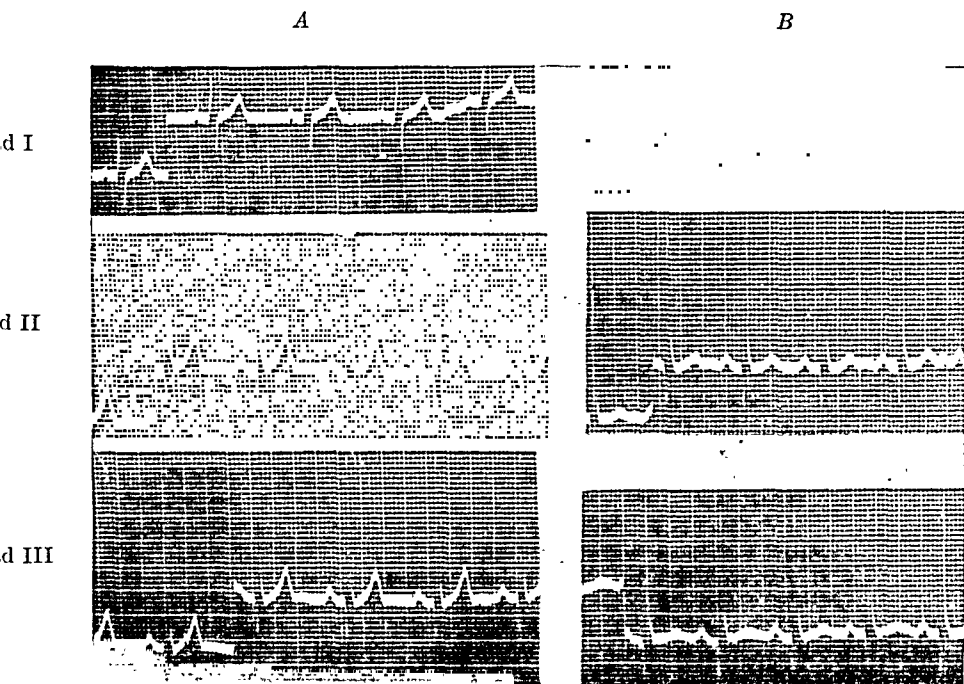


FIG. 1.—Case 18. *A*, control. *B*, shortly after injection of 50 cc. of 1% methylene blue, showing the depression of the *T* wave. At *B* there was 0.83 gm. % methemoglobin with a loss of 7.1% hemoglobin.

was noted. Likewise, methylene blue does not appear to attack the automatic and conductive tissues directly, since no definite changes were found in the *P-R* or *Q-R-S* interval, nor were *A-V* block, bundle-branch block or irregularities in rhythm found. Our observations indicate that methylene blue may have a direct action on the ventricular musculature.

There was usually a slight increase in respiratory rate and a sense of oppression in the chest, with some difficulty in breathing. Occasionally there was a dull pain over the heart. No appreciable rise or fall in blood pressure was observed. A moderate acceleration of the heart rate was present, similar to that observed by Stammers¹¹ in dogs.

Soon after starting the injection the skin and mucous membranes became bluish. Restlessness, apprehension and fine fibrillary tre-

mors of the face and extremities developed. A sense of "burning" in the mouth and warmth in the stomach was always present and this was occasionally accompanied by nausea and vomiting. When vomiting occurred the gastric contents were found to be stained blue. The saliva was also tinted blue, corroborating the findings of Rembridge, Hanke, and Halpert¹² that methylene blue is secreted by the stomach and salivary glands as well as by the liver¹³ and kidneys. Abdominal pain was occasionally noted.

A number of subjects became excited by the injection: in one case the pupils dilated and the individual had a feeling of impending death; in another, at the height of the injection, everything went black before his eyes and he started to perspire profusely. One individual, more apprehensive than usual at the start of the injection, complained of severe pain in the chest with a feeling of weight on the sternum; became very excited and, owing to the symptoms of impending collapse, the injection was stopped at 25 cc. Paresthesias were noted as an early complaint in every case. A number of individuals complained of slight nausea, dizziness, headache, and mental confusion for about 12 hr. following the injection. These effects have been entirely temporary and without any serious result.

Dr. Norman Jolliffe of the Psychiatric Division of Bellevue Hospital was kind enough to allow us to refer to a patient who was admitted in a psychotic condition following the use of O₂ and CO₂ by inhalation and an intravenous injection of methylene blue for carbon monoxide poisoning. The patient was restless, noisy, had to be restrained in a straight jacket and was disoriented as to time and place. She remained mentally confused and hyperactive for about 4 days. It was the impression of the Psychiatric Staff that this condition was a result of methylene blue poisoning.

Most of the drug is eliminated by the kidneys and it usually required from 3 to 5 days for the dye to be eliminated by this route. Urine containing methylene blue is irritating and excites frequency, burning, and painful micturition. Two individuals complained of severe burning in the scrotum and groin before the injection of 50 cc. of methylene blue was completed.

Untoward effects at the site of injection similar to those obtained with arsphenamin may result if the injection is made in part into the sheath or subcutaneous tissue.

Discussion. At first sight it would seem that the picture presented could be explained as due entirely to anoxemia, as it is well known that methylene blue produces methemoglobin.^{17, 17, 14} Certain observations are, however, distinctly opposed to such a view. Although we are not in a position to know how great a reduction in hemoglobin would be necessary to produce such a clinical picture if it were due to anoxemia, we do know that Haldane, Makgill and Mavrogordato¹⁵ found that as much as 6% of the blood pigment in rabbits could be changed to methemoglobin without producing any symptoms. Furthermore, Dautrebande¹⁶ found no significant

change in cardiac output until the hemoglobin approached 50%, and Harrison and Blalock¹⁷ until blood amounting to about 3% of the body weight of the dog had been lost. The maximum loss of hemoglobin that we found at the height of the symptoms was only 8.3% of the total hemoglobin (Table 1), and in 2 cases, in which the symptoms and electrocardiographic changes were of the usual magnitude, the decrease was negligible (0.6 and 0.4%). We are therefore led to conclude that the observed decrease in hemoglobin is not proportional to the intensity of the symptoms.

Although the number of cases studied permits only a qualitative interpretation of the data, it is evident that the magnitude of change in the $\text{Fe}^{++} \rightarrow \text{Fe}^{+++}$ system is too slight to consider it responsible for the clinical picture obtained, unless it be argued that the reversibility of this reaction is almost immediate. If the condition which we have described was due to methemoglobinemia, it would hardly seem possible that the blood taken at the height of the symptoms would not show more methemoglobin (Table 1). However, Stadie¹⁸

TABLE 1.—AMOUNT OF METHEMOGLOBIN FORMED AND PER CENT LOSS OF HEMOGLOBIN FOLLOWING THE INJECTION OF 50 CC. OF A 1% SOLUTION OF METHYLENE BLUE.

Case.	Hemoglobin control, Gr. %.	Decrease in hemoglobin after injection, Gr. %.	Methemoglobin present after injection, Gr. %.	Loss of hemoglobin expressed as % of total hemoglobin.
12	15.7	1.0	0.7	6.4
14	12.8	0.8	1.3	6.0
15	14.3	1.2	1.3	8.3
16	13.0	0.1*	0.9	0.6
17	11.7	0.1*	0.7	0.4
18	13.4	1.0	0.8	7.1

* Within limit of experimental error which was equivalent to 0.1 gr. %.

says that methemoglobin is destroyed rapidly in the circulating blood, but that when 30 to 50% of the total hemoglobin is changed suddenly following intravenous injections of sodium nitrite, methemoglobin may be found in the blood. Therefore, the possibility of demonstrating methemoglobin in clinical cases would seem slight and may account for the negative results reported by Geiger¹⁴ and the relatively small amounts found in our cases.

Furthermore, the clinical picture is not truly comparable to the one found in anoxemia. If this condition were brought about by acute anoxemia, a more marked effect on respiration and circulation^{19,20} than what we found would certainly be expected. Lewis and Matheson²¹ found that heart block occurred regularly during acute anoxemia in cats and dogs. Although Kountz and Gruber,²² Ward and Wright¹⁹ and Greene and Gilbert²⁰ in their electrocardiographic studies found a decrease in amplitude of the *T* wave during moderate anoxemia, similar to our observations with methylene blue, in our cases, as we have shown, anoxemia played nowhere near so important a rôle as it did in theirs. We are led to conclude that the harmful effects of methylene blue should not be associated

essentially or chiefly with methemoglobin, but rather attributed to disorders of function due to the direct action of the drug itself.

Conclusions. 1. Our observations indicate that methylene blue, under the conditions of this study, has two actions. The first of these is the oxidation of hemoglobin to methemoglobin. The amount of methemoglobin found immediately following the injection of the average therapeutic dose is small.

2. The second is that this drug, used intravenously, excites the individual and by its rapid elimination into the stomach and urine produces transitory gastro-intestinal and urinary irritation. The most frequent toxic symptoms observed were restlessness, paresthesias, a sense of "burning" in the mouth and stomach, pain in the chest and strangury. These manifestations usually subsided in 24 to 48 hours. Leakage of a small amount of methylene blue about the vein gives rise to a very painful infiltration.

3. Electrocardiographic studies show that methylene blue produces a reduction in the height or even reversal of the *T* wave frequently with lowering of the *R* wave. This suggests depression of the ventricular musculature.

4. The amount of methemoglobin found and the subsequent decrease in hemoglobin is not of sufficient magnitude to account for the clinical picture described on the basis of anoxemia.

5. We therefore wish to point out that the indiscriminate use of methylene blue may produce unpleasant results and be dangerous to the patient.

We are indebted to Dr. Arthur C. DeGraff for valuable suggestions in connection with this work.

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THE THERAPEUTIC EFFICACY OF BISMUTH SUBNITRATE IN ARTERIAL HYPERTENSION.

BY CURTIS BRUEN, M.D.,

NEW YORK.

(Experiment carried out in the Adult Cardiac Clinics of Beth Israel Hospital and the Hospital for Joint Diseases.)

ADEQUATE control in the investigation of therapeutic results in arterial hypertension, as has been emphasized by Ayman,^{1,3} requires

an adequate regulated period of pre-treatment observation, uniform clinical conditions during control and experimental periods, and the determination of the effect of non-specific therapy. These provisions are necessary in order to estimate the spontaneous lability of the blood-pressure, and the effects on the blood-pressure of the experimental procedure. The effects of such factors as frequency of visits, rest periods, and non-specific medication can be individually determined in separate experiments, and subsequently allowed for in interpreting the apparent results of therapy. Both the spontaneous variability of the blood-pressure in response to uncontrolled environmental, physical and psychic conditions apart from clinical observations, and the response incidental to the special conditions of controlled experiment, under which the effect of therapy is to be investigated, can thus be preliminarily determined, and corrected for in the final interpretation of therapeutic results. But this leaves it still necessary to evaluate the change occurring during an experimental period by inference from remote changes which occurred during control periods. Unrecognized adventitious factors may intervene to invalidate such inferences.

Experimental Method. Yet it is possible so to organize the experimental procedure that the chemistry of the experimental and non-specific medications alone differentiates control periods from experimental periods. A standardized procedure for determining the blood-pressure, uniform frequency of visits during control and experimental periods, and the effect of non-specific therapy can be provided for. Only two variables, apart from the long-time trend which may be neglected, remain: adventitious influences and therapeutic actions. Their effects can readily be distinguished. By alternating control periods under non-specific medication, not sensibly different from the experimental medication, with experimental periods under experimental medication, any alteration in the blood-pressure, which occurs during a period of experimental medication, can be referred either to adventitious factors or to the medication according to its continuance or cessation upon the resumption of non-specific medication. Such a procedure makes possible the prosecution of vigorously controlled experimentation on the effects of therapeutic agents in arterial hypertension.

Bismuth subnitrate by mouth has been utilized in dosages up to gr. x, 3 times a day, in the treatment of arterial hypertension by Stieglitz,² who, in summarizing his results in extensive, though inadequately controlled, series, reported that the average systolic and diastolic pressures reverted far toward the maximum normals for the average age. In a smaller series, in which control factors were allowed for, Ayman³ found bismuth subnitrate in such dosage to be without demonstrable effect on the blood-pressure.

Bismuth subnitrate by mouth was found in extensive tests on a subject with normal arterial tension to produce prolonged and

effective reduction of the blood-pressure.⁴ Bismuth subnitrate by mouth, by reason of its presumptive nitrite action, would therefore appear to merit adequately controlled application in arterial hypertension to definitively evaluate its therapeutic efficacy. An experimental procedure appropriate to this purpose was elaborated.

Method. The standardized method for determining the blood-pressure consisted in making and recording on a specially designed chart (Chart I) 10 successive readings at each visit. This procedure was regarded as more applicable and practical than the use of rest periods, since it conforms more closely to ordinary clinical usage, can be more uniformly employed and consistently regulated, and requires less psychic adaptation and compliance of the patient. While each reading was being charted the air was allowed to escape freely from the cuff in order that distal circulation might be reestablished. The time of beginning and concluding each determination was recorded to the nearest half minute. The interval covered by a blood-pressure determination was $3\frac{1}{2}$ or 4 min. in most instances, but ranged from $2\frac{1}{2}$ to $5\frac{1}{2}$ min., depending upon immediate manipulative requirements, and particularly the height of the systolic pressure.

Only blood-pressure determinations made at weekly intervals were regarded as significant and comparable. The respective clinics were held early Monday and Wednesday evenings, with the exception of three Tuesday mornings at one and a Tuesday evening at the other, to avoid greater derangement, or interruption, of the experimental routine by holidays. The patients were seen in turn after variable waiting periods, the length of which depended upon immediate clinical exigencies; but, since the individual patients tended to habituate themselves to coming each week at the same hour, they tended to be seen regularly at about the same time and after uniform waiting periods. At each visit a detailed interval history was taken and a physical examination done in accordance with the standard record-form used in the clinics. The patients were seen exclusively by one physician, who urged the necessity of regular weekly visits, listened with patiently sympathetic interest to all complaints and unburdenings, and evinced a candidly encouraging attitude in responding to inquiries regarding clinical progress.

During a 3-weekly-visit foreperiod, the patients were kept on the lactose-tablet placebo regularly used as control medication in the clinics, in order to permit of comparison of the blood-pressure determinations made according to the special method of the experiment with the blood-pressures recorded during previous observation, and to render the period of previous observation available as a supplementary control period.

Subsequently 3-weekly-visit control periods on non-specific medication consisting of cerium oxalate in amounts grossly equivalent to the prospective dosages of the experimental medication were alternated with 3-weekly-visit experimental periods on bismuth subnitrate. Cerium oxalate was chosen as the non-specific medication, because it is an inert substance having only inert impurities, and in consistency and appearance superficially resembles bismuth subnitrate. Cerium oxalate proved adequate as the control medication inasmuch as but one patient more or less consistently inquired of the occurrence or discontinuance of a slight seeming pinkness and sweetness in the medication after it had in fact been changed, and only one other intimated at one time that she had made a comparison of a left-over sample of a past medication with the present medication and noted a difference.

Three successive experimental courses in which the graded dosages of cerium oxalate of gr. vii, gr. xv, and gr. xxii corresponded to the graded dosage of bismuth subnitrate of gr. x, gr. xx, and gr. xxx were prosecuted.

The medication was dispensed in boxes containing the exact number of powders to be taken before the succeeding visit. The powders were prescribed to be taken 3 times a day, apportioned approximately every 8 hrs. to conduce to an even distribution through the 24 hrs. The hour of the last medication before each visit was asked and recorded to encourage the regular taking of the medication, to insure medication before visits, and to define the interval between the last medication and the registration of its possible effect. This interval ranged from 3 to 6 hrs., but was usually 4 hrs.

Material. Patients newly assigned or carried under the diagnosis of hypertension, unselected except with regard to their maintenance of cardiac compensation and regular sinus rhythm, were entered into the experimental series as they became available. All who proved amenable to the experimental routine were retained, except those who registered diastolic pressures regularly below 90, or who were eliminated through the development of heart failure or prolonged intercurrent illness. The final series (Table 1) consisted of 20 cases, 1 male, 19 females, in 15 of whom all 3 experimental courses were completed, in 3 the first 2 courses, and in 2 only the first course. Two were new patients; 5 were in the first 6 months, and 5 in the second 6 months of observation; 3 were in the second, 3 in the third, and 2 in the fourth year of observation.

Their age ranged from 27 to 73 with a median of 51 years. The stated known duration of hypertension ranged from a few months to 19 years with a median of 3 years. Their average control systolic/diastolic pressure ranged from the minimum of 139/97 to the maximum of 258/137 with a median of 164½/113. The changes in their

LEGENDS FOR CHARTS I AND II.

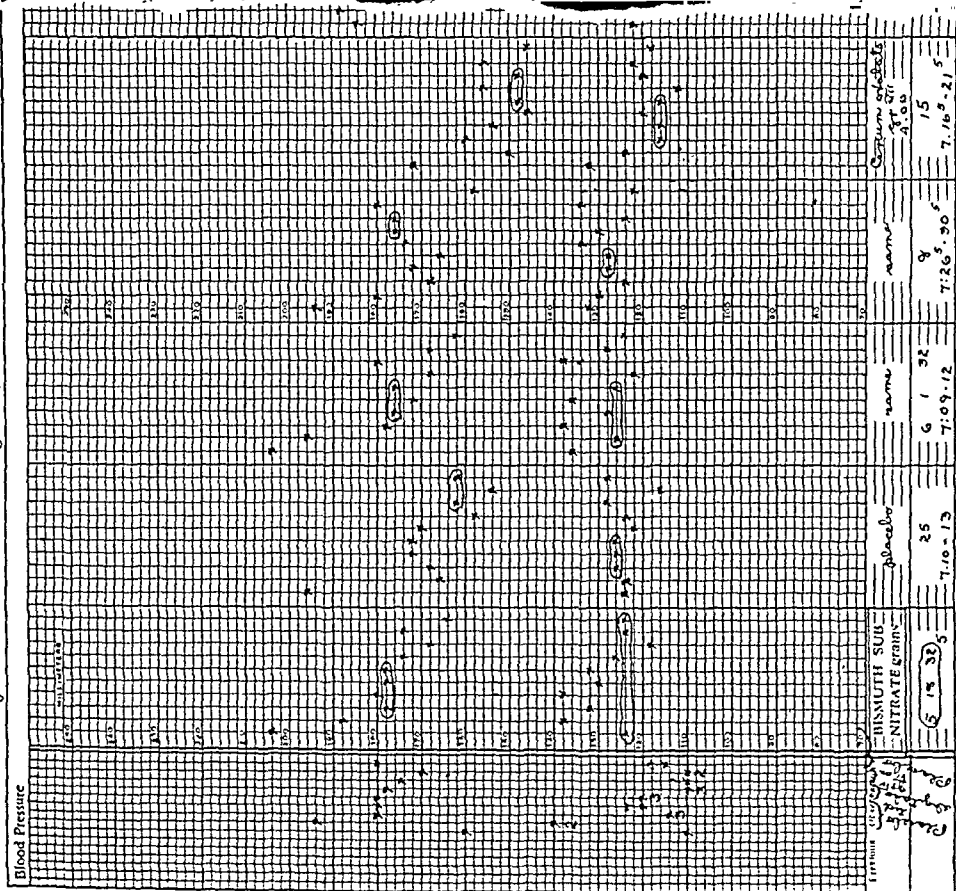
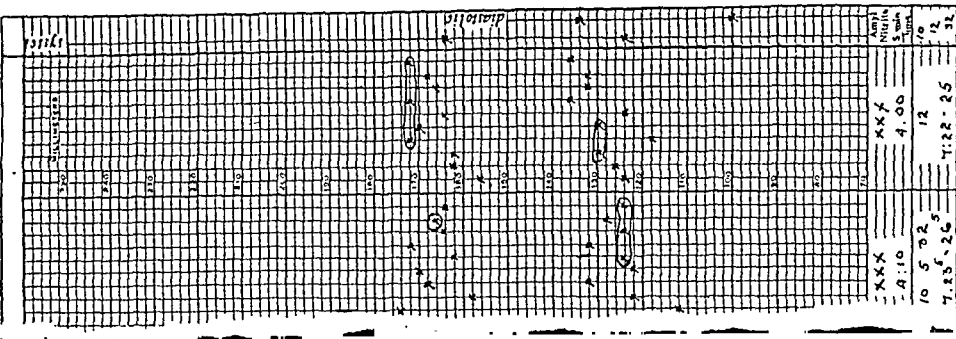
CHART I.—Blood-pressure record chart. The section to the left of the double line reproduces the blood-pressure readings recorded during the period of previous observation. The mode of the 10 successive blood-pressure readings recorded on each visit during the experiment, indicated by being enclosed in a circle, represents the result of the determination. The medication taken during the interval preceding the visit, together with the time of taking the last dose, and the date, together with the times of beginning and completing the blood-pressure determination, are recorded below the blood-pressure readings. In the subsection on the extreme right, the blood-pressure before and after the inhalation of amyl nitrite is recorded.

CHART II.—Graphic case records. The ordinates represent the blood-pressure in millimeters of mercury; the abscissæ represent successive visits. Each of the 20 large rectangles represent the course of the blood-pressure in the case designated by the number in its upper right-hand corner. Weekly visits during the period of previous observation are indicated by black dots, fortnightly by circles, other visits by circles with numerals subscribed to designate the number of weeks. When, during the period of previous observation, more than one blood-pressure reading was recorded at a visit, the first reading is indicated by being included in the graph of the trend. For the period of the experiment, each level of the blood-pressure recorded in the 10 successive readings of a determination is indicated by a circle, and their mode by a black dot. The trends of the maximum, modal, and minimum pressures are indicated by graphs. The small empty rectangles indicate dosages of cerium oxalate, the blackened rectangles dosages of bismuth subnitrate. Gaps in these rectangles indicate interruption of medication and extensions of the interval between visits. The arrow-tipped vertical lines represent the response to the inhalation of amyl nitrite.

Case 16

Age 39

Name Burr, Harry



Medication

Date

Duration of hypertension from May 1930

Chart I.

M.D.

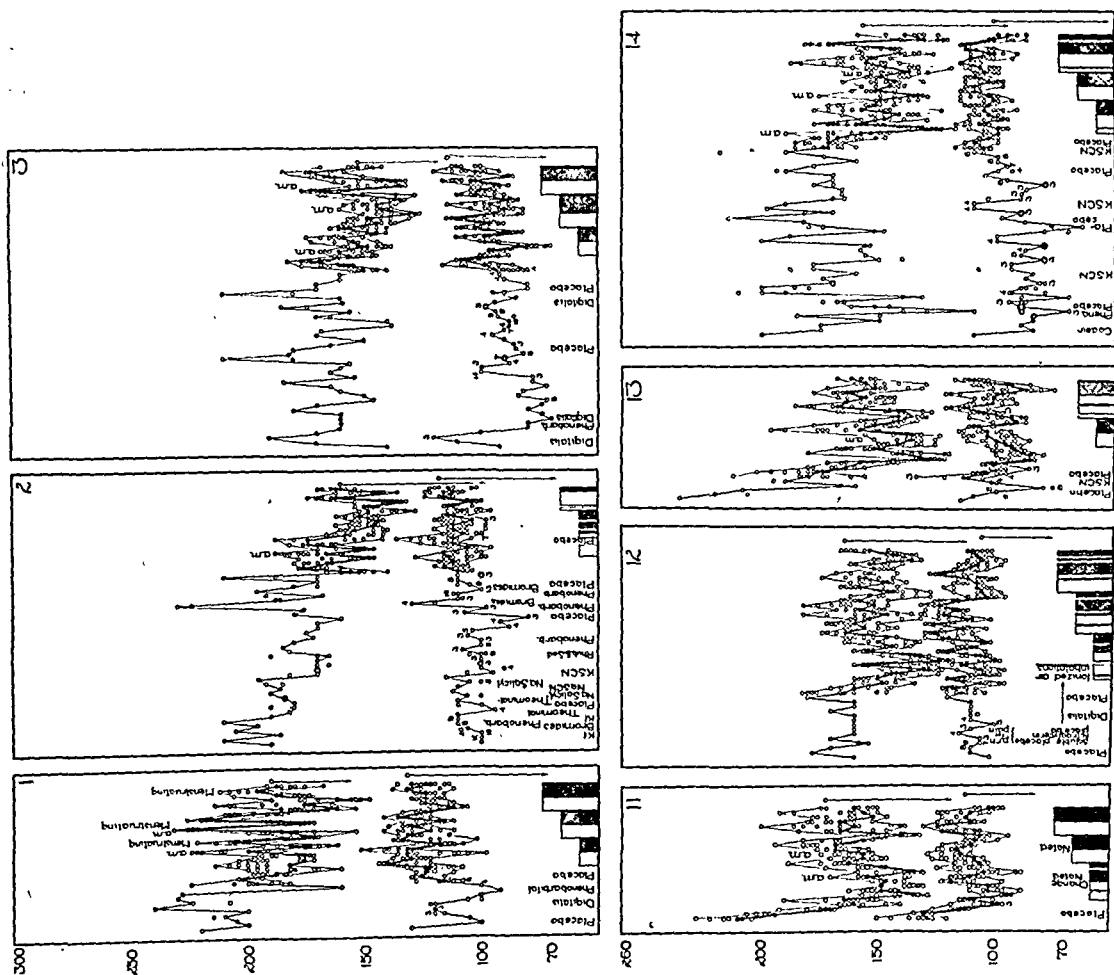


CHART II.

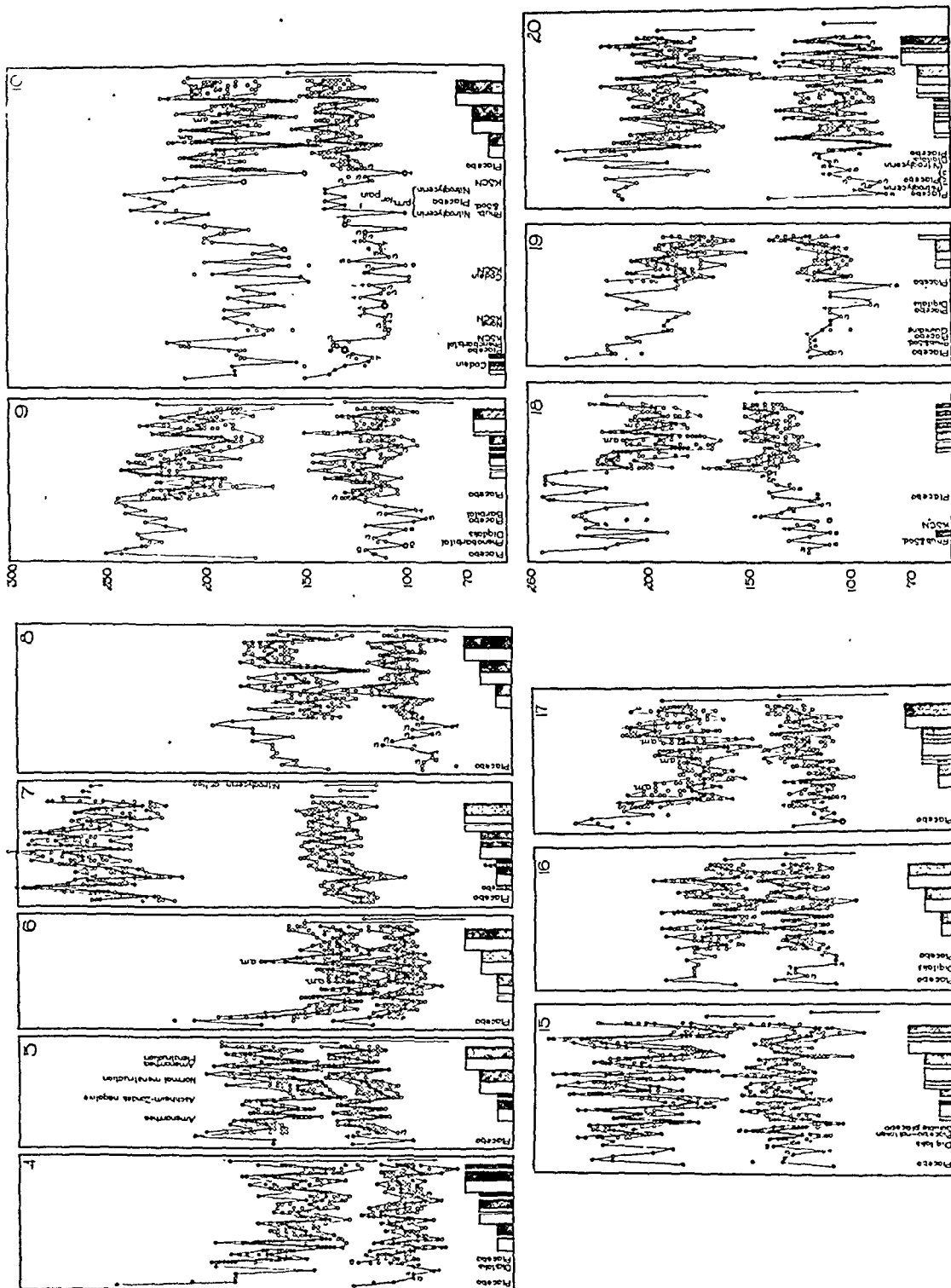


CHART II.—Continued.

TABLE 1.—BISMUTH SUBNITRATE BY MOUTH IN ARTERIAL HYPERTENSION.

Cases.	Name.	Sex.	Age.	Percentile difference from average weight.*	Diagnosis:	Anatomic†	Physiologic†	Functional†	Accompanying condition.	Psychic status.	Years prior observation.	Resistance of peripheral arteries.	Changes in retinal arterioles.	Average control blood pressure.	Blood pressure after amyl-nitrite.	Blood-pressure variation.	Alteration of symptoms.
1	SG JD	♀	36	+1	Hyp	EH SA	RSR	Ila	Non-toxic goiter	Intensified affective drive	3½	0.5	Increased light reflex	181/127	156/72	Continued slight downward trend; wide fluctuation systolic, moderate diastolic	Asymptomatic generally, occasionally transitory symptoms only.
2	AcC JD	♀	50	+3	Hyp	EH	RSR	Ila	Neurasthenia; emotional and psychomotor instability	Neurasthenia; emotional and psychomotor instability	19	3.9	Increased reflex, slightly roughened outline	156/112	98/68	Continued slight downward trend; psychogenic rises level; moderate fluctuations	Full varied complement of over-elaborated symptoms.
3	AH JD	♀	52	+44	Hyp	EH SA	RSR	Ila	No abnormality indicated	Depression, self-dramatizations, compensatory reactions	14	2.7	Widened reflex, slightly roughening	157/105	118/72	Continued slight downward trend; psychogenic rises level; moderate fluctuations	Practically continuous cumulative psychogenic exacerbations.
4	RB BI	♀	70	+21	Hyp	EH SA	RSR	Ila	Emotional instability	Depression, self-dramatizations, compensatory reactions	2	0.7	Increased reflex, slightly roughened outline	166/125	142/82	Initial upward trend, during which amenorrhea developed; sharp drop after negative Aschheim-Zondek; upward trend	Repeated psychogenic exacerbations.
5	GH BI	♀	27	+49	Hyp	EH	RSR	Ila	Emotional instability	Depression, self-dramatizations, compensatory reactions	6	0.2	Slight nodular narrowing	139/105	100/74	Initial upward trend, during which amenorrhea developed; sharp drop after negative Aschheim-Zondek; upward trend	Erratic variation in severity and extent.
6	MD JD	♀	57	-25	Hyp	EH	RSR	Ila	Regressive non-adjustive reactions to acute difficulties	Regressive non-adjustive reactions to acute difficulties	1	0.2	Increased reflex, nodular narrowing, compression veins	276/122 262/118 (236/144)	276/122 262/118 (236/144)	Fluctuation within narrow range, occasional elevated elevations trend	More typical symptoms continuous; psychogenic variable.
7	BA BI	♀	50	+48	Hyp	EH SA	RSR	Ila	Hysterical choreic attacks	Hysterical choreic attacks	6	0.9	Increased reflex, nodular narrowing, smaller bulging veins	153/105	116/82	Slightest downward trend systolic; slight upward trend diastolic; moderate fluctuations	General improvement, occasional psychogenic attacks.
8	FM BI	♀	57	+36	Hyp	EH	RSR	Ila	Slight emotional instability	Slight emotional instability	3	1.8	Increased reflex, smaller narrowed, compressed veins	208/119	116/82	Slight upward trend systolic, fluctuation fluctu-tolic, irregular fluctuation without trend	Alternately improvement and exacerbation.
9	RG BI	♀	43	+3	Hyp	EH	RSR	Ila	No abnormality indicated	No abnormality indicated	Increased reflex, slightly roughened, bulging veins	157/131	120/84	Essentially without change.	Asymptomatic, except inter-attack periods with moderate psychogenic exacerbations.

2 2.7 ++

Increased reflex, slightly roughened, indentation

Asymptomatic, except inter-attack periods with moderate psychogenic exacerbations.

10	JB JD	♀	55	+2	Hyp	EH	RSR	Ila	Diabetes mellitus	Emotional instability; depression with over-reaction; undefined phobia, largely pathophobia, suppressed during waking by Mental Science, rampant during sleep	3	0	2.7	++	Increased reflex, slightly narrowed, moderately tortuous, indentation veins	187/131	126/84	Slight downward trend systolic, upward diastolic; irregular, slightly cyclic, fluctuation	Asymptomatic, save intermittent paresthesias and neuralgias, probably on basis diabetic neuritis, but apparently with psychogenic incidence.
11	SC JD	♀	48	+10	Hyp	...	RSR	F	...	Slight psychomotor tension	3	0	2.7	±	Slightly narrowed and tortuous, slight indentation veins	160/113	118/82	Marked decline during fore-period; subsequent slight upward trend, irregular or cyclic fluctuation	Marked initial improvement, subsequent variation.
12	AnC BI	♀	39	+4	Hyp	EH	RSR	Ila	...	No abnormality indicated	1½	1.1	1.1	++	Moderate narrowing, slight tortuosity	150/113	112/76	Irregular fluctuation without trend	Slight cumulative increase.
13	GS JD	♀	50	+15	Hyp	EH	RSR	Ila	...	No abnormality indicated	3	0.4	0.4	-	Moderate to extreme narrowing, compression veins	151/100	Early adaptive decline, subsequent cyclic fluctuation	Essentially unchanged.
14	EA JD	♀	73	+27	Hyp	EH	RSR	Ila	...	No abnormality indicated	3	2.7	2.7	±	Moderate narrowing, slight tortuosity, indentation veins	154/107	96/64	Early slight decline systolic, subsequent narrow fluctuation	General improvement, especially first months.
15	LH BI	♀	47	+24	Hyp	...	RSR	E	...	Emotional instability	2	0.6	0.6	+	Narrowing, tortuosity, indentation	202/133	140/88	Wide totally irregular fluctuation without trend	General aggravation, psychogenic increment.
16	HB BI	♂	30	+17	Hyp	EH	RSR	I	...	Neurasthenia: hysterical conversion symptoms	1½	0.6	0.6	±	Much narrowing, slight tortuosity, medullated nerve fibers	163/127	124/100	Wide fluctuation without trend, twice higher on bismuth substrate	Preponderant improvement.
17	FMel JD	♀	45	-11	Hyp	EH	RSR	Ila	...	Diffuse persecutory paranoid trend	½	0.5	0.5	-	Great narrowing, much tortuosity, indentation veins	183/121	124/82	Initial decline, repeated upward trends terminated by falls	Generally unchanged, psychogenic exacerbations.
18	AM JD	♀	61	+23	Hyp	EH	RSR	I	Diabetes mellitus	No definite abnormality indicated	4	3.7	3.7	+	Extreme narrowing; light reflex veins	203/137	170/96	Irregular fluctuation without trend	Paresthesia lower quadrants; diabetic neuritis.
19	IK BI	♀	46	0	Hyp	EH	RSR	I	...	No abnormality indicated	1½	1.1	1.1	++	182/111	Narrow fluctuation systolic, upward trend diastolic	Initial improvement, subsequent aggravation.
20	RK BI	♀	63	0	Unk	EH	RSR	Ilb	...	Possible incipient senile dementia; querulous over disabilities	4	1.0	1.0	+	Very extreme narrowing, perivasculitis, choroidoretinitis	192/106	146/86	Wide irregular fluctuation	Generally unchanged, several brief exacerbations.

* Mellico-Actuarial Mortality Investigation, New York, vol. 1, 1912.

† Abbreviations, initials or first letters of: Hypertension, Arteriosclerosis, Unknown, Enlarged Heart, Sclerosis of Aorta, Coronary Sclerosis, Aortic Insufficiency or Stenosis, Mitral Insufficiency or Stenosis, Regular Sinus Rhythm.

‡ Code letters: I = Able to carry on habitual physical activity. Ila = Slightly diminished physical activity. Ilb = Greatly diminished physical activity. E = Possible heart disease. F = Potential heart disease.

retinal arterioles ranged by fine gradations from a minimal increase of the light reflex to extreme narrowing with perivascularitis. The peripheral arteries on palpation were in 5 of normal resistance to compression, in 6 of probably increased resistance not sufficient in degree to be definitely assignable to the vessel wall rather than to its internal pressure, in 6 of definitely increased resistance, and in 3 of markedly increased resistance.

The response to the inhalation of amyl nitrite^{5,4,3} was determined in 18 cases (Chart II). Drastic drops in the systolic and diastolic pressures occurred in all but 1 case. This case, which gave only slight and equivocal responses in repeated trials with amyl nitrite and nitroglycerin, registered the highest blood-pressure in the series, showed only an intermediary degree of narrowing of the retinal arterioles, and presented scarcely any definitely increased resistance of the peripheral arterial walls. Neither the absolute nor the relative extent of the response in the remaining cases showed any relationship to the anatomical condition of the radial arteries or the retinal arterioles.

Cardiac hypertrophy occurred in 17 cases. One gave physical signs of aortic valvular lesions, 1 of a mitral lesion, and 2 of combined lesions. Renal involvement of a degree requisite to occasion nocturia was indicated in 18 cases, a tendency to subcriterional specific gravity in 14, traces of albumin in 14, and hyaline casts in 4. An accompanying condition of non-toxic goiter occurred in 1 case, of diabetes mellitus in 2. One gave a history of arrested lues. All had negative blood Wassermann tests.

They, being poor women, were hard beset. No directed effort was made to investigate their psychic status. But in the course of the incidental observation of their behavior on the part of the physician, and the inevitable unburdening on the part of the patients, incident to prolonged clinical observation, sufficient data accrued to assess the psychic status in almost all cases, and to assign diagnoses of minor psychic abnormalities in $\frac{2}{3}$ of the cases. Outright neurasthenia occurred in 2, hysteric manifestations in 3, conditions approaching psychasthenia in 3, and independent or concomitant intensification or instability of affective tone in 7.

Results. The blood-pressure reading nearest the apparent mode of the 10 successive readings was designated as the result of each blood-pressure determination (Chart I). The variation of this modal blood-pressure was regarded as representative of the variation of the blood-pressure during the course of the experiment. The blood-pressure in the several cases pursued a great variety of individual courses (Table 1; Chart II). Its fluctuations were invariably attributable to adventitious factors. In no instance did a drop in the blood-pressure, significant on comparison with the control values, correspond with or accompany the administration of bis-

muth subnitrate. *Throughout bismuth subnitrate was without demonstrable effect on the blood-pressure.* The previous observation of reduction of the blood-pressure in arterial hypertension,⁴ made in the absence of the control of immediately preceding non-specific medication, was not confirmed.

The symptoms, dyspnea, palpitation, cardiac pain, dizziness, and headache, described in terms both of their absolute degree and its comparison with that of the preceding visit, because they appeared to be most easily evaluated and most literally reported by the patients, were selected, together with any particularly prominent individual symptoms, as a basis for the generalization of the symptomatic course during the experiment (Table 1). The symptoms also pursued an independent course without reference to the administration or withdrawal of bismuth subnitrate. Bismuth subnitrate was without apparent effect on the symptoms.

Samples of freshly voided urine collected on the last visit of each control period, and on the first and last visits of each experimental period, were immediately tested for nitrite by the addition of sulphanilic acid— α -naphthylamin acetate reagent. With rare exceptions, distributed proportionately between control and experimental periods, the urine tested negative for nitrite. Bismuth subnitrate did not give rise to the excretion of nitrite in the urine.

Summary and Conclusions. 1. Adequate control in the investigation of therapeutic results in arterial hypertension requires provision for both the spontaneous lability of the blood-pressure and the effect of the experimental procedure itself on the blood-pressure.

2. When the experimental procedure is so organized as to provide a standardized method of blood pressure determination, uniform frequency of visits, and the alternation of control periods under non-specific therapy with experimental periods under experimental therapy, any alteration in the blood-pressure which occurs can be either attributed to adventitious factors or interpreted as a therapeutic effect.

3. Such an experimental procedure is self-contained, inasmuch as its control periods are adequate for comparison with its experimental periods, independently of any period of previous observation.

4. Such an experimental procedure, directly applicable to any therapeutic agent that acts without delay, cumulative effects, or retention, and adaptable to therapeutic agents different in these respects, was devised and applied to the investigation of the therapeutic efficacy of bismuth subnitrate.

5. Bismuth subnitrate by mouth, even in the largest therapeutically practicable dosage, does not develop sufficient nitrite action to exert any demonstrable effect on the blood pressure or symptoms of arterial hypertension under the conditions of rigorously controlled experiment.

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THE IONTOPHORESIS OF ACETYL-BETA-METHYLCHOLIN CHLORID IN THE TREATMENT OF CHRONIC ARTHRITIS AND PERIPHERAL VASCULAR DISEASE.*

PRELIMINARY REPORT.

BY JOSEPH KOVACS, M.D.,

ASSISTANT IN MEDICINE, NEW YORK POST-GRADUATE MEDICAL SCHOOL OF COLUMBIA
UNIVERSITY; ASSISTANT PHYSICIAN, DISPENSARY, NEW YORK POST-GRADUATE
HOSPITAL, NEW YORK, N. Y.

(From the Arthritis and Vascular Clinics of the Department of Medicine of the New
York Post-Graduate Medical School and Hospital of Columbia University.)

THE discovery that cholin compounds relieve vascular spasm and increase peripheral circulation induced me to experiment with them in chronic arthritis, where we deal generally with disturbed circulation, and in the spastic types of peripheral vascular disease.

The importance of circulatory disturbances in chronic arthritis is generally recognized and it is believed by many to be an essential factor in causing and maintaining a rheumatic condition. The poor circulation may be considered as an etiologic factor in this symptom complex, although definite proof in this regard is still lacking.

It was found by Wright and Pemberton,¹ Rhumann,² Lunedei and Corradini,³ and ourselves⁴ that disturbances of the circulation frequently accompany and undoubtedly aggravate chronic arthritis, hence the improvement of disturbed circulation plays a prominent rôle in the therapy of arthritis.

The usefulness of the acetyl-cholin group to increase peripheral circulation has been limited by the fact that it is rapidly destroyed by body fluids and blood. Recently another compound of cholin—acetyl-beta-methylcholin chlorid†—has been studied by Simonart.⁵ His investigation seems to indicate that acetyl-beta-methylcholin chlorid offers greater possibilities of clinical usefulness. He claims that it is destroyed more slowly in blood and body fluids, is more potent, and lacks almost entirely certain undesirable by-effects of acetyl-cholin. On normal persons and in peripheral vascular diseases, when administered subcutaneously, its action begins within 2 min. and ceases within 15 to 20 min. (Starr and collaborators).⁶

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† Synthesized by R. T. Major and J. K. Cline, J. Am. Chem. Soc., **54**, 242, 1932.

There is a slight fall of blood pressure, rise of pulse rate, flushing, sweating, and increased salivation. Administered by mouth its action begins within 15 to 75 min., lasts $\frac{1}{2}$ hour to 1 hour, and is much milder.

When drugs are administered in a diluted solution and given subcutaneously or intravenously, or taken by mouth, the effective ions are absorbed by the blood and distributed to all parts of the body, even though they are more needed locally. In the case of cholin compounds the local effect is greatly reduced because much of the drug is destroyed by the blood. In order to obtain a more effective local result the induction of acetyl-beta-methylcholin chlorid by iontophoresis (medical ionization) was attempted in the experiments herein reported.

In this method the ions are introduced locally from the surface, and there is only a slight general effect due to the absorption into the blood stream. Iontophoresis is accomplished by the use of galvanic current: if pad electrodes are soaked in a diluted solution of drugs and connected to a source of galvanic current, the ions of these drugs penetrate into the tissues under the effect of the suitable pole. The factors of the depth of penetration theoretically depend (1) on length of time the current flows, (2) on the electromotive force, (3) on the weight of the ions, and (4) on the tissues being treated.

Technique. A 1% solution of acetyl-beta-methylcholin chlorid (1 gm. in 100 cc. of water) is employed. The drug being an alkaloid with a positive charge, can be introduced into the tissues from the positive pole only. Reinforced asbestos fabric paper is saturated with the solution and wrapped around the affected joints. A fairly large malleable metal plate is placed over the wet asbestos paper and connected to the positive pole of a galvanic generator. A dispersive, very large, regular moist pad electrode is applied to the back or abdomen and is connected with the negative pole.

The current is turned on and slowly increased to 20 to 30 milliamperes, always being kept within comfortable toleration to the patient. Treatments of 20 to 30 min. are employed. To avoid the possibility of burns, care must be taken that the metal electrode or electrode clamps do not come in direct contact with the skin. The asbestos paper is more satisfactory than gauze or blotting paper for it absorbs less fluid and keeps moist for a longer time. We often treat two regions of the body at the same time, with the help of a bifurcated cable from the positive pole. After treatment, the part treated is dried and kept covered.

Physiologic Effects. *Local.* 1. "Gooseflesh," due to the contraction of the erector muscles of the hair follicles, was observed immediately after treatment and disappears within 10 to 30 min.

2. Sweating was observed immediately after treatment and continues for 8 to 10 hours. It is probably due to a direct action of the drug on the sweat glands, or their nerve supply.

3. Increase of skin temperature in cases where a spasm of the peripheral blood supply was present. The increase of temperature varied between 4 to 10° F. and remained for 2 to 4 hours.

4. Increase of rate of capillary flow without enlargement of the capillaries. The number of visible capillaries were not increased after treatment.

5. Slight redness of the skin which remained for 1.5 to 2 hours, due probably to the enlargement of the deeper small arteriole vessels.

6. Increased salivation when treatment was applied in the region of the salivary glands.

7. A questionable slight increase in the local leukocyte count was noted. Differential and total blood counts taken before and immediately after treatment from the treated part showed no change in the differential count, but a slight increase in the number of leukocytes (600 to 1000—in 1 case 3000). This was a constant finding but is recognized to be within the limits of error.

8. Warm feeling of the treated part for 24 to 72 hours; after repeated treatments, for longer periods; in some cases for a whole week.

9. In certain patients increased oscillometric readings were noted.

10. Reduction of swelling and increased mobility.

11. Relief of pain.

General Effect. When large areas were treated we often also observed a general effect causing flushing, sweating, increase of pulse rate and salivation, slight lowering of blood pressure and evidence of intestinal peristalsis. The intensity of these symptoms varied individually. They started generally after 1 to 10 min. and ceased right after the treatment was brought to an end.

Therapeutic Results. While this series of patients is too small and followed for too short a time to draw definite conclusions concerning the permanent value of the treatment, the results warrant presentation of evidence as a guide to future work.

Chronic Arthritis. Forty chronic rheumatic patients have been treated: 16 rheumatoid arthritics, 14 osteoarthritis, 3 cases of bursitis, 3 of sciatica, and 4 of neuritis.

In order to evaluate the obtained results, it was necessary to establish a principle on which to base conclusions. We regarded it as an improvement only if there was a definite reduction in pain, swelling and stiffness, with increase of function and lessening of deformities. Patients had for the first 3 to 4 weeks 2 treatments weekly, later 1. Most of the selected cases were old clinical patients who had previously had, in addition to general treatment, all other kinds of local treatment, such as diathermy, short-wave fever treatment, Roentgen ray treatment, etc., without relief of pains or improvement of symptoms. We did not change the form of general treatment, as we wished to gain a clear picture of the reaction of the iontophoresis.

The most promising results were obtained in the otherwise stubborn cases of rheumatoid arthritis; 95% of the cases showed improvement. These good results were anticipated in rheumatoid arthritis because this is the type of arthritis in which we have found the most pronounced circulatory disturbances. Two cases, after 2 months

of treatment, were symptom-free and have been without any complaint for the last 3 months, but most of the cases are still under treatment with improved condition.

In the osteoarthritic type the results were likewise encouraging. In this type of arthritis other therapeutic measures like heat, diathermy, massage, etc., had given satisfaction. With acetyl-beta-methylcholin chlorid iontophoresis there was a definite improvement in 80% of the cases.

There was full recovery in the 3 cases of sciatica, where diathermy and galvanic treatment had failed to give relief. All the sciatica cases were in a toxic or infectious stage without any changes in the bone structure of the spine.

In the 3 cases of bursitis 2 responded quickly but in the 3d case the treatment failed to give relief.

The 4 neuritis cases reacted well to the treatment and in every case there was a quick full recovery.

In both types of arthritis where the patients had definite swellings we observed after treatments a reduction of the swelling and an increased capillary circulation. Further studies are necessary to determine whether the increased capillary circulation is responsible for the reduction of swelling or whether the reduction of swelling relieving the tension of the tissues facilitates the capillary circulation.

This is not an attempt to create the impression that acetyl-beta-methylcholin chlorid iontophoresis is a specific therapy for chronic arthritis. Chronic arthritis must be considered as a systematic disease, with local manifestations in the joints. Treatment of the disease must be done primarily through systemic general measures, to which local measures are added. These local measures are equally important because they relieve painful and uncomfortable local symptoms of the patient and tend to prevent or ameliorate local organic changes. Acetyl-beta-methylcholin chlorid iontophoresis is a local therapeutic measure and thus far seems to promise more satisfactory results than other local therapeutic measures.

Peripheral Vascular Disease. It was felt that because of the physiologic effect and the clinical results of this treatment it might be of value in the treatment of the group of peripheral vascular diseases in which spasm is the chief factor.⁷ In the few cases treated desirable results have been obtained, namely, release of spasm with increased circulation. As noted by surface temperature, elevation and improvement of the capillary circulation; other symptoms also showed improvement. Chronic vascular ulcers have shown unusually rapid healing powers. This series is being further enlarged and studied and will be the subject of a later report.

In spite of the pronounced local action and good therapeutic results, we must admit that we still do not know precisely how much of the drug is absorbed by the tissues with the iontophoresis method and how deep the drug penetrates. Further investigation is needed

to explain the exact action of acetyl-beta-methylcholin chlorid iontophoresis on the local circulation and sweat glands.

That the effect of acetyl-beta-methylcholin chlorid iontophoresis is specific and not a simple galvanic effect was demonstrated in the following way: both hands of a patient were treated at the same time—one hand with the drug and the other with normal salt solution. Both hands were connected to the positive pole with the help of a bifurcated cable. The indifferent negative electrode was at the back. After 20 min. treatment with a 20 milliamperes strong galvanic current, the hand with normal salt solution remained cold. There was no sweating, only a slight redness in patches and the capillary picture remained unchanged. The hand treated with the drug showed all the characteristic symptoms of acetyl-beta-methylcholin chlorid iontophoresis; as increased skin temperature, sweating (which continued 6 to 10 hours), gooseflesh, faster capillary flow and a slight diffuse redness.

The effect of acetyl-beta-methylcholin by iontophoresis is not confined to a skin area, and hence is quite different from a simple counter irritant. The general reaction points to the absorption of the drug into the general circulation. The therapeutic effect of this form of treatment might be explained by the deposition of the drug in the superficial tissues and its slow absorption from there, giving prolonged slight general vasodilatation, combined with a pronounced and prolonged local effect.

Conclusions. 1. A preliminary report on the action of the iontophoresis of acetyl-beta-methylcholin chlorid is presented.

2. Acetyl-beta-methylcholin chlorid introduced locally with the help of the galvanic current produces a pronounced and prolonged local effect which cannot be obtained through subcutaneous or oral administration.

3. This local treatment appears to be of value in chronic arthritis, especially in the rheumatoid type.

4. This treatment may also be of value for patients with peripheral vascular disease in which spasm is an important factor.

5. No harmful general effects were observed.

6. Further studies with prolonged observation of cases, especially in view of the fallacies lurking in the evaluation of the therapeutic test, are essential for the correct evaluation of this method.

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THE BONE MARROW IN IDIOPATHIC THROMBOPENIC PURPURA.

By JOHN S. LAWRENCE,
ASSOCIATE PROFESSOR OF MEDICINE,

AND

RALPH E. KNUTTI,
INSTRUCTOR IN PATHOLOGY, UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE
AND DENTISTRY, ROCHESTER, NEW YORK.

(From the Departments of Medicine and Pathology, University of Rochester School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial and the Rochester Municipal Hospitals.)

REMARKABLY few studies of the bone marrow in idiopathic thrombopenic purpura have been reported.^{3,4,7,11,12} All of these reports, except that of Minot,⁷ have presented evidence of abnormalities of the megakaryocytes and thus have given substantial support to the theory of Frank² as to the pathogenesis of this condition. Notwithstanding this fact, the prevailing opinion in American textbooks of medicine is that there are no changes of note as regards the megakaryocytes in the bone marrow in this disease. Minot and Buckman¹ make a statement to the effect that the few human cases studied postmortem "show no decrease in the number of megakaryocytes, which suggests that defective formation of platelets does not necessarily occur in this idiopathic form of the disease." Sturgis⁸ states that "the bone marrow does not show characteristic changes; there does not appear to be a reduction in the number of megakaryocytes." No statement as to the bone marrow in this condition is made in Osler and McCrae's *Principles and Practice of Medicine*.¹⁰ On the other hand, Naegeli⁹ holds that a bone marrow disorder lies in the forefront in this condition.

In view of the fact that the studies which have been made on the bone marrow of patients with this disorder have been few and have not led to uniform results, we have been studying during the past 3 years morphologic characteristics of the bone marrow of a small series of patients with this type of purpura. The sternal marrow has been studied in most of our patients, as this was found to be the easiest to obtain from living subjects. The marrow from other locations was studied postmortem in a few cases. The marrow has been found to be essentially normal in 4 of 6 patients with the typical findings of idiopathic thrombopenic purpura. In the other 2 patients the megakaryocytes were diminished in numbers and appeared abnormal.

Methods and Results. We have relied mainly upon the findings in sections of marrow stained with hematoxylin and eosin. Other stains—Giemsa, Jenner-Giemsa, Wright's and supravital neutral red, have been used also in part of the cases. We regret that complete studies of this nature were not made in all of our patients. Such stains are now included in the routine study of all of the specimens of marrow removed from the sternum in this clinic.

Case Reports. CASE 1.—M. W. (Unit No. 31010). Married woman, aged 31, presented the typical history and clinical findings of chronic idiopathic thrombopenic purpura—repeated epistaxis, purpuric lesions in skin, profuse menstrual bleeding. The red blood cell count was 4,580,000 per cmm. The hemoglobin was 75% (Sahli). The white blood cell count was 7350 per cmm. and the differential count was normal. The blood platelets were markedly reduced, a fixed stained smear showing about 1 normal platelet per oil-immersion field. The bleeding time was 6 min. The coagulation time (test-tube method) was 15 to 18 min. The clot was very friable and broke upon an attempt being made to pick it up.

A specimen of marrow was removed from the sternum. A section of this stained with hematoxylin and eosin showed no apparent decrease in the number of the megakaryocytes and no morphologic abnormalities of these cells. The eosinophilic myelocytes were not increased. The other marrow cells were present in proportionately normal numbers. Smears stained with Giemsa and Jenner-Giemsa stains revealed an entirely normal picture.

Impression. Normal bone marrow. Chronic idiopathic thrombopenic purpura.

CASE 2.—E. P. (Unit No. 52088). Married woman, aged 36, had a classical history for chronic idiopathic thrombopenic purpura. The laboratory findings were typical of this condition, the only unusual finding being a persistent leukopenia. The number of leukocytes varied between 1620 and 6600 per cmm. (average of 46 determinations, 3633). Repeated differential counts revealed normal percentages of the various white blood cells. The number of the red blood cells varied between 3,140,000 and 5,180,000 and the percentage of hemoglobin between 60 and 103 (Sahli). The percentage of reticulocytes remained low, the highest figure being 6 and the lowest 1.2. The bleeding time was prolonged, 6, 8, $12\frac{1}{2}$, 23, $27\frac{1}{2}$ and $30\frac{1}{2}$ min. The coagulation time was 8 to 14 min. (test-tube method). The clot was friable and did not retract.

Bone marrow, removed from the sternum on December 10, 1931, and stained with hemotoxylin and eosin, showed abundant marrow cells. There was no appreciable reduction in the number of the megakaryocytes and morphologically, these cells appeared to be normal. The eosinophilic myelocytes were numerous and seemed to be slightly increased in numbers. The other cells appeared to be normal.

Impression. Normal bone marrow. Chronic idiopathic thrombopenic purpura.

CASE 3.—S. B. (Unit No. 26047). Married woman, aged 23, whose illness was characterized by evidence of a hemorrhagic diathesis—bleeding from gums, nose and vagina. The duration of the illness was 3 months. She was under observation in the Rochester Municipal Hospital during the last 3 weeks of life. The red blood cell count remained between 1,610,000 and 2,400,000 per cmm. The hemoglobin varied between 24 and 40% (Sahli). The number of the white blood cells fluctuated between 16,050 and 12,300 per cmm. The differential counts were normal. The percentage of reticulocytes was 10 on one occasion and 5.7 on another. The platelets were markedly reduced, none being found in a fixed stained preparation on two occasions and only a very few on another. The coagulation time (test-tube method) was 8 to 12 min. There was no clot retraction. The clot was rubbery and elastic. The bleeding time was greater than 30 min. Blood was found in both urine and stool specimens. The patient died 23 days after admission to the hospital.

Autopsy. The bone marrow from the midfemur was uniformly dark red. All fat seemed to have been replaced. A section stained with hematoxylin and eosin revealed evidence of a moderately hyperplastic marrow. The megakaryocytes were quite numerous. They varied in size, many of

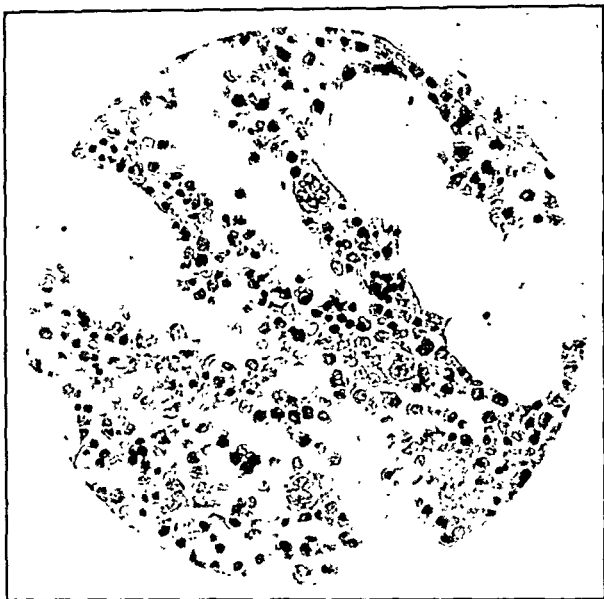


FIG. 1.—A typical field from a section of marrow from the femur of Case 4. Hematoxylin and eosin stain. ($\times 430$.) Note the presence of megakaryocytes with large vesicular nuclei.



FIG. 2.—A typical field from a section of the sternal bone marrow of Case 5. Hematoxylin and eosin stain. ($\times 430$.) Three megakaryocytes are present; 2 of these have heavy staining close-textured nuclei.

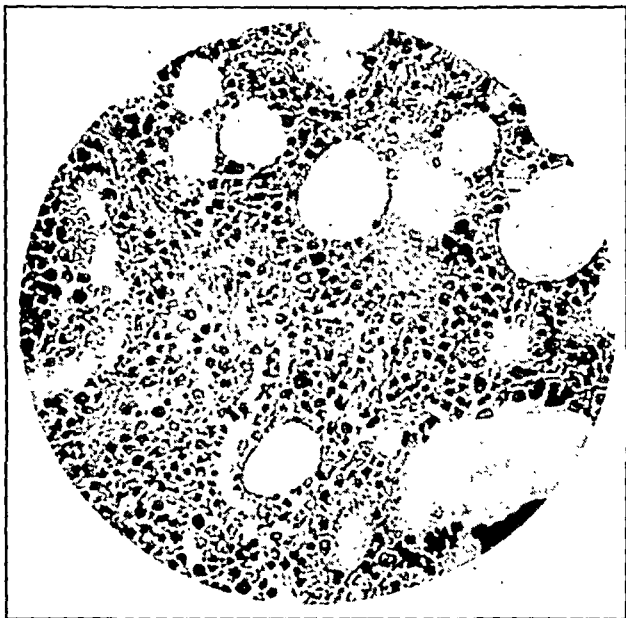


FIG. 3.—A typical field from a section of the sternal bone marrow of Case 6. Hematoxylin and eosin stain. ($\times 250$.) No megakaryocytes are present.

them being only about $\frac{1}{2}$ as large as usual. Most of these smaller cells had shrunken, dark-staining irregular nuclei with a small amount of pink cytoplasm. Most of the larger megakaryocytes had small, round, clear nuclei with abundant pale cytoplasm. A few of them showed shrunken, dark-staining nuclei with more deeply pink cytoplasm. Eosinophilic myelocytes were not relatively increased in numbers. The other marrow cells, though abundant, showed no distinct changes.

Impression. Hyperplastic bone marrow with morphologic variations of the megakaryocytes. Acute idiopathic thrombopenic purpura.

CASE 4.—S. M. (Unit No. 24234). Widow, aged 48, gave a history of generalized purpura for 5 weeks and tarry stools for a few weeks. On the morning of admission she suddenly developed twitching of the left forearm and hand and then became paralyzed. She became comatose and died the day after admission. Her red blood cell count was 3,000,000 per cmm. The hemoglobin was 65% (Sahli). The white blood cell count was 7500 per cmm. and the differential count was normal. No platelets were found in a fixed smear stained with Wright's stain. The capillary clotting time was 5 to 6 min. The clot did not retract. The urine gave a strongly positive guaiac test.

Autopsy. The bone marrow from the middle of the right femur was grayish-red and seemed to have retained only a small amount of the usual fat. The marrow of the lumbar vertebræ was pale grayish-red. That of the ribs was diminished in amount and had a pinkish-gray color. Sections from the ribs, vertebræ and femur (Fig. 1) were stained with hematoxylin and eosin. The marrow was of normal amount. Frequent megakaryocytes were present. Most of these were large cells with a uniformly pink cytoplasm and with numerous round to oval clear finely stippled nuclei. Very few were noted with deep blue nuclei. Eosinophilic myelocytes seemed slightly increased in numbers. The other cells showed no abnormalities.

Impression. Slightly hyperplastic bone marrow. Acute idiopathic thrombopenic purpura.

CASE 5.—R. T. (Unit No. 47855). Unmarried male, aged 19, gave a history of recurrent severe epistaxis for 2 years. For 10 days he had had generalized purpuric areas. His red blood cell counts varied between 4,660,000 and 5,100,000 per cmm. with hemoglobin values between 80 and 90% (Sahli). The white blood cell counts fluctuated between 3500 and 7200 per cmm. The differential counts were normal, the neutrophils representing 57 to 76% of the cells. The percentage of reticulocytes was 3. In fixed stained smears, the platelets were absent or very rare. The bleeding time was greater than 1 hr. The coagulation time (test-tube method) was 12 min. The clot was soft and jelly-like.

A specimen of sternal bone marrow was removed on March 21, 1932. A section of this stained with hematoxylin and eosin was not entirely satisfactory, due to the small amount of marrow. However, the number of megakaryocytes appeared less than normal and a good percentage of those present had heavy-staining nuclei of the close-textured type. Supravital neutral red, Giemsa and Jenner-Giemsa preparations showed less megakaryocytes than normal. The other marrow cells appeared normal (Fig. 2).

Impression. Reduced number of megakaryocytes in the bone marrow. Chronic idiopathic thrombopenic purpura.

CASE 6.—R. K. (Unit No. 75955). Unmarried man, aged 41, had had ecchymoses and numerous petechiæ on frequent occasions for 15 years. On one occasion he had had slight bleeding from the gum. Epistaxis had occurred only occasionally. His red blood cell count was 2,970,000 per cmm. The hemoglobin was 10.5 gm. per 100 cc. The reticulocytes were 0.1%. The volume of packed red blood cells was 35.4 cc. The mean corpuscular volume was 119.2 cc. The mean corpuscular hemoglobin was

35.3γγ. The mean corpuscular hemoglobin concentration was 29.6%. The white blood cell count was 4200 and the differential count was normal. There was about 1 platelet to each 6 to 8 oil-immersion fields in a fixed smear stained with Wright's stain. The bleeding time was 5 to 8 min. The coagulation time (test-tube method) was 8 min. The clot retracted poorly.

A specimen of marrow was removed from the sternum (Fig. 3). Sections of this stained with hematoxylin and eosin revealed a relatively abundant cellular content. The eosinophilic myelocytes appeared to be increased in numbers. The number of the megakaryocytes was markedly diminished, only 3 or 4 being found in each section. Only one of these appeared normal. The others showed a very scanty cytoplasm. Their nuclei were dark blue, shrunken and finely granular. The other marrow cells appeared normal.

Impression. Reduced numbers of megakaryocytes in the bone marrow. Chronic idiopathic thrombopenic purpura.

Discussion. Our observations are not wholly in accord with either of the two more important theories (Frank², Kaznelson⁵) as to the mechanism responsible for the diminished number of platelets in the peripheral blood of patients with idiopathic thrombopenic purpura. The failure to find any abnormal changes of note in the bone marrow of 4 of the patients supports the contention of Kaznelson that the primary disorder is not in the bone marrow. The fact that the morphologic appearance of the bone marrow presented no marked changes does not prove, however, that the marrow was functionally normal. Nevertheless, from these findings it would be impossible to say that the platelets were not destroyed after entering the peripheral circulation and that the spleen was not probably the most important center for this destructive process.

The presence of diminished numbers of megakaryocytes in 2 of the cases presenting the typical picture of idiopathic thrombopenic purpura supports Frank's original idea that the primary disorder lies in the bone marrow. The cases reported by Seeliger,¹² Jedlicka and Altschuller,⁴ Schmincke¹¹ and Gerlach³ further support this theory. Finally the findings in 1 of our patients (not included in this report) who had an aplastic marrow at death but who several months previously had had marrow which was capable of regeneration is in conformity with Frank's theory. Our impression is that this patient had marked aplasia of the megakaryocytes and slight aplasia of the granulocytes when first observed. Later the red cell function of the marrow was involved also and aplastic anemia resulted.

In view of the fact that our observations have shown clear-cut evidence of bone-marrow involvement in some patients with idiopathic thrombopenic purpura and in others no involvement of the marrow, we are inclined to think that there are at least two different types of this condition insofar as the bone marrow is concerned. Lescher and Hubble⁶ have previously made a suggestion of this same nature. We have felt that those cases of chronic idiopathic thrombopenic purpura which presented normal morphologic bone-marrow findings would be more likely to profit by splenectomy than would those who had an abnormal bone marrow. Our series of

cases is much too small to justify any positive assertion in this connection. It would seem to us advisable to have sternal bone-marrow studies on all such patients prior to operation. If such observations are recorded in various clinics, it may be possible to determine whether the prognosis as regards the effect of splenectomy can be more correctly evaluated by knowing the bone-marrow picture.

It may be stated here that we have never encountered any trouble from removing marrow from the sternum of patients with diminished numbers of platelets and abnormal coagulating mechanisms. In addition to the cases here reported, we have removed bone marrow from the sternum of several additional individuals, some of whom had symptomatic thrombopenic purpura. We have always either given the patients a transfusion before operation or else have had a donor available in case of bleeding after operation. As a routine measure, we would suggest that the sternal marrow be removed within 48 hours after transfusion and that a donor be on hand in case postoperative bleeding should occur.

Conclusions. 1. The bone marrow in idiopathic thrombopenic purpura may present no abnormal morphologic characteristics or it may show changes as regards the megakaryocytes.

2. It is suggested that there may be two types of this disease on the basis of the bone-marrow picture.

3. The question has been raised as to the probable value of bone-marrow studies in regard to determining the prognosis from splenectomy in patients with chronic idiopathic thrombopenic purpura.

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MEGAKARYOCYTOSIS IN WHITE MICE WITH SPONTANEOUS MAMMARY CARCINOMAS.

By W. C. HUEPER,
PHILADELPHIA, PA.

THE origin and histogenesis of extramedullary megakaryocytes in the organs of the human adult have been for some time the subject of a lively discussion (Petri,¹ Downey, Palmer and Powell²).

Some investigators (Aschoff,³ Lubarsch,⁴ Goroncy⁵ and others) claim that the heterotopic occurrence of these cells in the lung, liver, spleen, kidney and lymph nodes is always of an embolic nature caused either by a mechanical trauma to the bone marrow (fracture) or resulting from a hyperactivity of this tissue, in the course of which megakaryocytes are swept out into the circulation (septicemia, pneumonia) (MacCallum⁶) (polycythemia, leukemia). Other workers, however, maintain that extramedullary megakaryocytes are, at least in part, of autochthonous origin, especially in conditions accompanied by heterotopic hematopoietic foci (leukemia, pernicious anemia, etc.) (Koerner,⁷ Naegeli,⁸ Barth,⁹ Morawitz and Denecke,¹⁰ and others); that is, in diseases which are characterized by the reappearance of myeloid cellular elements in organs, from which they normally disappear toward the end of fetal life (Schridde¹¹). This conception is supported by the experimental results of Kuczinski¹² and Custer,¹³ who used mice and rabbits respectively in their work.

During certain investigations upon white mice with spontaneous mammary cancers, a high incidence of extramedullary megakaryocytes in various organs was noted, thereby substantiating the observations previously made by Hill¹⁴ and Waterman.¹⁵ Considering, moreover, the fact that cancer-bearing mice rather often show extramedullary lymphoid and myeloid foci in various organs, which sometimes reach leukemoid proportions (Jaffé,¹⁶ Hill,¹⁴ Simonds,¹⁷ and others) and are, therefore, comparable to those pathologic conditions of the human hematopoietic system, which are not infrequently associated with heterotopic megakaryocytosis, the carcinomatous mouse appears to be a suitable source for collecting additional information on the origin and histogenesis of heterotopic megakaryocytes.

The present communication is based upon the histologic examination of the organs of 210 white mice, 172 of which had spontaneous mammary carcinoma, while 38 were normal white mice of the same strain. Of the cancer mice 91 and of the normal animals 19 had been subjected to Roentgen ray treatments of varying intensity, the total doses, ranging from 40 r to 6000 r in the different animals, delivered over a period of from 1 to 6 weeks. Twenty-one cancer animals were untreated and had died a natural death, while the remaining animals had received at some time during their lifetime injections of various kinds of organic and inorganic chemotherapeutic substances.

In view of the fact that megakaryocytes and small accumulations of myelocytes are often present in moderate number in the spleen of normal mice and considering that, as has been mentioned before, these elements are usually found in increased numbers in the spleens of carcinomatous mice, the description of the effects of the various treatments given may be restricted to those types of treatment

which produced changes in these normal conditions. It was noted that in a series of 31 cancer animals and 19 normal mice the application of Roentgen rays (1000 *r* to 6000 *r*) caused a more or less complete disappearance of the hematopoietic tissue in the organs of the majority of these animals. The application of smaller doses especially of very small ones (30 *r* to 90 *r*), over a prolonged period and at longer intervals, seemed to have resulted in an increase in the amount and incidence of myeloid tissue in various organs, confirming the observations of Fischer-Wasels and Buengeler¹⁸ and others.

The series treated with the various chemical agents did not show any appreciable differences from the conditions seen in untreated animals.

A histologic examination was made of the following organs: Tumor, lung, heart, liver, pancreas, spleen, lymph nodes, kidney, suprarenal gland and brain. All sections were carefully studied for the presence of megakaryocytes. A longitudinal section was made through the spleen, or in cases with markedly enlarged spleens, the section was prepared from $\frac{1}{2}$ of the spleen. Splenic enlargements were rather frequent in the carcinomatous mice and sometimes reached huge proportions. The relative frequency of megakaryocytes in the spleen was determined from the histologic study of the sections and was recorded in the following manner: none, 0; scanty, +; moderate, ++; many, +++; very numerous, ++++. A similar type of evaluation of splenic megakaryocytes was recently used by Waterman.¹⁵

If the 172 spleens of the carcinomatous series are grouped according to the frequency of megakaryocytes, the following compilation is obtained:

	0	+	++	+++	++++
Cancer series	18 (11)*	11 (5)	61 (9)	58 (5)	23 (1)
Tar cancer series of Waterman	3	8	9	9	5
Normal series	11	6	8	10	3
Tar refractory series of Waterman	9	8	8	2	2

* The numbers in parentheses designate animals which had been exposed to heavy irradiation with Roentgen rays. The destructive effect of the rays upon the megakaryocytes is obvious.

These figures illustrate well the high incidence of megakaryocytes in the spleen of mice with spontaneous carcinoma and compare well with those obtained by Waterman¹⁵ in mice with tar cancers and in mice refractory to tar.

The increase in the number of splenic megakaryocytes in the cancer mice is to a certain extent reflected in the incidence of these cells in other organs. In 36 mice megakaryocytes were found in extrasplenic locations: 25 times in the liver alone, in 6 instances in the liver and lung and once in liver and kidney, twice in the lung and twice in lymph nodes.

Heterotopic megakaryocytes were found in:

	Times.
Liver	32
Lung	8
Lymph node	2
Kidney	1

A certain parallelism exists between the occurrence of extrasplenic megakaryocytes and the number of these cells in the spleen.

	Frequency in the spleen.				
	0	+	++	+++	++++
Extrasplenic megakaryocytes in:					
Cancer mice	0	1	11	12	4
Normal mice	0	1	0	1	2

The extrasplenic megakaryocytes in the normal series were found in 3 instances in the liver and once in a lymph node.

The compilations given above show quite definitely that heterotopic megakaryocytes in white mice are most numerous in the spleen and liver and are far less so in the lung and kidney. This observation concerning the relative frequency and distribution of heterotopic megakaryocytes in mice agrees well with that made by Koerner⁷ in a case of myeloblastic leukemia, where the largest number of megakaryocytes was observed in the spleen, liver and lymph nodes, while they were much less numerous in the lung and kidney.

Goroncy,⁵ however, found in his series of 27 cases of extramedullary megakaryocytosis quite different numerical relations. Megakaryocytes were present in the lung 17 times, liver 14 times, spleen 9 times. He noted, moreover, that these cells were most numerous in the lung.

The marked contrast between the observations of Goroncy⁵ and those made by us in mice suggest that heterotopic megakaryocytes found in mice do not all represent cell emboli of medullary origin, but are at least in part of local genesis. This conception receives additional support from other observations (Kuczinski; Custer; Downey, Palmer, and Powell and others).

Though Goroncy found that many of the extramedullary megakaryocytes consisted only of bare nuclei, the cytoplasm supposedly being stripped off during their passage through narrow vessels, the megakaryocytes seen in the spleen, liver and lymph nodes of mice were usually well preserved and without any signs of mechanical cellular destruction, indicating that these cells had not been exposed to such trauma (Siegmond²³).

It was furthermore noted that the megakaryocytes in the spleen were not infrequently grouped in smaller and larger clusters, similar to those seen in the bone marrow as the result of regenerative megakaryocytic proliferation. Considering the fact that these megakaryocytic accumulations consisted of young and old cells, their embolic nature appears to be unlikely.

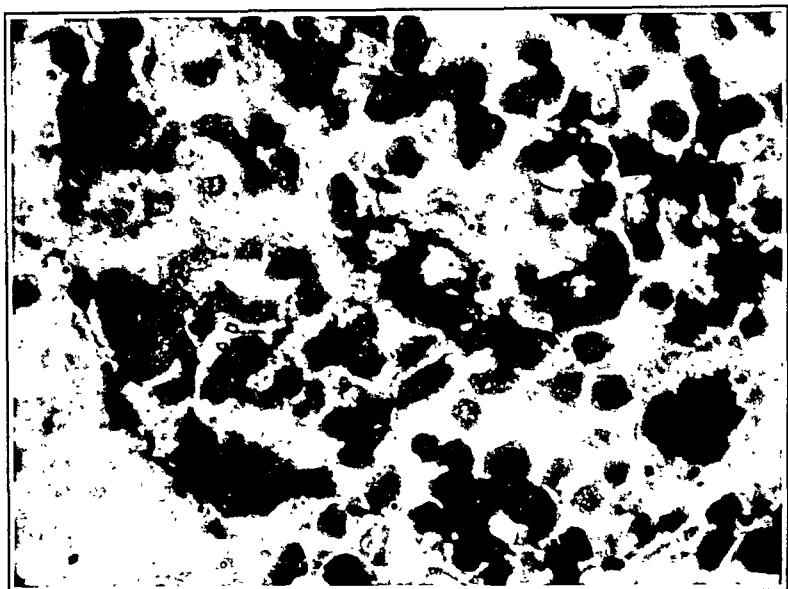


FIG. 1.—Megakaryocytes and transitional cell forms in the spleen.

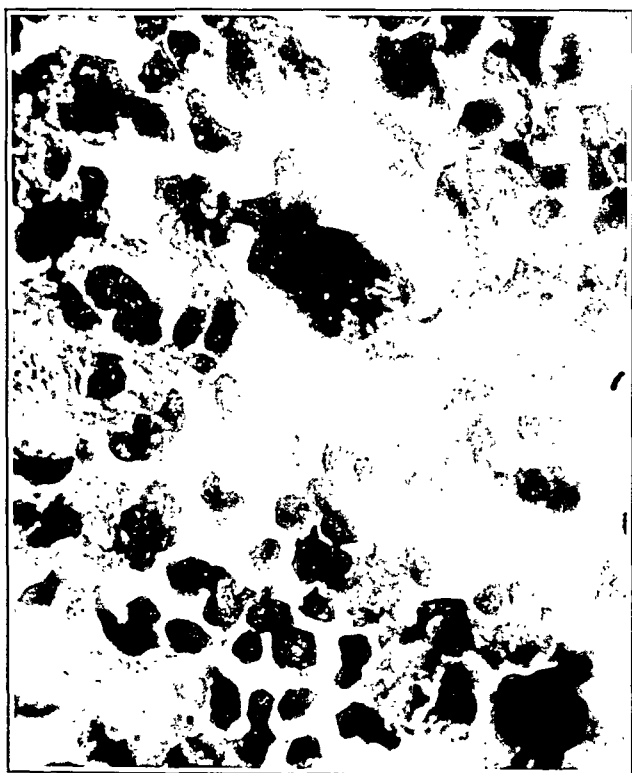


FIG. 2.—Megakaryocytes forming part of the cell lining of a sinus in the spleen.



FIG. 3.—Megakaryocytes in the dilated capillary lumina in the liver. Kupffer cell proliferation.

The existence of local relations between the occurrence of heterotopic megakaryocytes and extramedullary myeloid foci (Koerner,⁷ Waterman,¹⁵ Askanazy¹⁹) may be regarded as additional circumstantial evidence against the conception of an exclusive medullary origin and embolic distribution of these cells. It is known that in the normal spleen of the adult mouse megakaryocytes and myelocytes are often found coëxisting, *i. e.*, a condition persists during postembryonic life which is found in the human spleen and liver only during fetal life. Also an increase of megakaryocytes in the spleen and a reappearance of these cells in the liver and lymph nodes of the adult, and especially of the cancerous, white mouse is in general accompanied by an increase of the myeloid elements in the spleen (Hill¹⁴) and by the formation of smaller and larger myeloid foci in the liver and lymph nodes of these animals.

It has been argued that these heterotopic myeloid elements always originate from extravascularly implanted young blood cells derived from the bone marrow. But this conception completely disregards the numerous observations made in regard to the persistence of developmental potentialities in certain types of vascular cells during adult life (Maximow,²² Askanazy¹⁹). In numerous livers of the carcinomatous mice the Kupffer cells were in a state of active proliferation and myeloid cell groups were found in the dilated lumina of the capillaries. There were also smaller and larger foci of reticular tissue with hematopoietic function located in close connection with the walls of the hepatic veins.

The numerical relations existing between the frequency and distribution of extramedullary megakaryocytes and the occurrence of heterotopic lymphoid and myeloid foci is illustrated in the following tabulation, extrasplenic megakaryocytes being represented by the numbers in parentheses.

	Splenic megakaryocytosis.				
	0	+	++	+++	++++
Lymphoid foci in 1 or several organs	6	5	41 (7)	21 (7)	14 (3)
Increased myeloid tissue in spleen	1	3	3	7 (1)	0
Myeloid foci in liver, lymph node and lung	1	3 (2)	11 (4)	28 (8)	13 (4)
No heterotopic lymphoid or myeloid foci	10	1	5	1	1

Beside this strong circumstantial evidence in favor of the local genesis of heterotopic megakaryocytes, the histologic examination of the spleen, liver and lymph node furnished confirmatory information of a more direct and conclusive character.

The spleens containing numerous megakaryocytes always showed evidence of more or less proliferative activity of the reticulum and reticuloendothelial cells. Usually there were in the pulp large numbers of round, moderately sized and fairly uniformly shaped cells which had a moderately large amount of cytoplasm and rather large vesicular nuclei with conspicuous interlacing chromatin

threads. These were regarded as free reticular cells. Cells of similar morphology were found in the sinuses together with evidence of proliferation of the lining cells. These cells were especially prominent in spleens with marked atrophic, fibrotic and amyloidotic changes, as they then frequently represented a predominant cell type on account of the simultaneous relative scarcity of lymphoid and myeloid cell elements. In spleens with lymphoid or myeloid hyperplasia the reticular cells were found intermingled with the respective mature and immature lymphoid and myeloid cell forms, the latter being easily recognizable by their ring-shaped nuclei.

Megakaryocytes were noted in varying numbers in the pulp and sinuses of the spleen. In some spleens they appeared to be more common in the subcapsular zone and in the neighborhood of the trabeculae, where also accumulations of myeloid cells were most frequently found. They often occurred in small groups and clusters which were usually composed of giant cells in different stages of maturation intermingled with cells of an evidently transitional type (between reticulum and reticuloendothelial cells and well-developed young megakaryocytes). The mature megakaryocytes had a large segmented or nodulated nucleus of pyknotic, highly chromatic character and a large mass of an irregularly and usually not sharply contoured, eosinophilic cytoplasm. In less mature giant cells the nucleus was more compact and often indented on one side, resembling that of a monocyte in shape, and was surrounded by a more or less basophilic, distinctly outlined cytoplasm. Central rarefactions were common in these nuclei. The cytoplasm was in general well and sharply outlined in the free cells and smaller in amount than that of the mature cell. This is apparently the form which Duesberg²⁰ has designated as "lymphoid" and which v. Boros and Korenyi²¹ have called "megakaryoblast." In degenerating megakaryocytes, the nucleus seemed to have broken into several fragments. The outline of the cell was indistinct and highly irregular. Hyaline masses without nuclei or with a few chromatin granules represented completely degenerated giant cells, which were in some spleens quite numerous.

Many of the megakaryocytes found in the pulp seemed to be interconnected by delicate threads or compact plasmatic bridges with the adjacent reticulum cells, with which they apparently formed a syntetial mass. Transitional forms of various stages between the reticulum cells and completely developed megakaryocytes were not rare, especially in the neighborhood of groups of megakaryocytes. During the early part of the transformation of a reticulum cell into a megakaryocyte there was only a diffuse general hypertrophy of the nucleus and cytoplasm of the reticulum cell noticeable. With the increasing swelling the cells showed a large, but rather compact nucleus, usually of round shape. Cells representing the next step in the megakaryocytic development of

reticulum cells resembled those described above as the "megakaryoblastic" form.

The endothelial cells lining the sinuses were apparently another source of megakaryocytic formation. Here enlarged and swollen cells projecting into the sinusoidal lumen were not infrequently observed. Sometimes 2 large swollen cells were found back to back, 1 protruding into the sinus, the other into the surrounding pulp. Cells possessing all the morphologic characteristics of megakaryocytes were often seen forming an integral part of the lining of sinuses. This type of development could be especially well followed in spleens with marked fibrotic and amyloidotic changes which emphasized the sinusoidal structure of the organ. The lymph follicles were always free from megakaryocytes.

Free forms of megakaryocytes of different degree of maturity were not only noted in the pulp and sinuses, but also in the lumens of the larger splenic veins. In 1 instance, 2 giant cells were found in the leukemic blood of a medium-sized vein passing through the pancreas. These observations indicated that megakaryocytes formed in the spleen can be the source of embolic megakaryocytosis in other organs.

In the liver the megakaryocytes were mainly located in the lumens of the sinusoidal capillaries. The cells seemed sometimes to be attached to the sinusoidal wall by plasmatic processes. This was often noted in livers which showed a marked proliferation of the Kupffer cells. The latter cells were swollen in some instances and protruded into the lumen, resembling in many respects the transitional forms found in the spleen. Extracapillary megakaryocytes were occasionally seen between the cells of perivascular myeloid infiltrations.

The megakaryocytes observed in the lymph nodes, which always contained myeloid foci, seemed to have the same genetic relations to the reticulum cells as those which have been described for the spleen.

The lung was, as has been stated above, quite often the seat of megakaryocytes. They were found lodged in the capillaries, bulging their walls into the alveolar lumen on both sides of the inter-alveolar septum. Their nuclei were always dark, pyknotic, markedly segmented and surrounded by little or no cytoplasm. The myeloid and lymphoid perivascular and peribronchial infiltrations were always free of these cells. The same observation was made in the myeloid and lymphoid foci in the kidney. The megakaryocytes found in the kidney were lodged in the glomerular capillaries.

These observations are important evidence in confirmation of the autochthonous origin of heterotopic megakaryocytes in white mice and support the claims of Custer,¹³ Downey, Palmer and Powell² and Lignac²⁴ in regard to the derivation of these cells from both reticular and endothelial elements of the reticuloendothelial system.

The present investigation can add very little to the question of the causative mechanism of heterotopic megakaryocytic proliferation. The relatively frequent coëxistence of amyloidotic changes in the spleen and liver or both and extrasplenic megakaryocytosis suggests the possibility that toxic agents are also involved in the stimulation of megakaryocytic proliferation.

	Splenic megakaryocytosis.				
	0	+	++	+++	++++
Amyloidosis in spleen . . .	2	3 (2)	6 (2)	10 (3)	7 (1)
Amyloidosis in liver . . .	2	0	8 (5)	16 (5)	7 (3)

The numbers put in parentheses designate animals with extrasplenic megakaryocytosis.

While among 125 mice without amyloidosis 20 had an extrasplenic megakaryocytosis, 47 mice with amyloidosis showed this phenomenon in 16 cases.

The extent of the malignant growth as determined by the presence or absence of internal metastasis (heart, lung) had apparently no bearing upon the frequency and distribution of heterotopic megakaryocytes.

Conclusions. 1. In addition to extramedullary megakaryocytes of embolic origin (lung, kidney), autochthonous megakaryocytes also occur in various organs (spleen, liver, lymph nodes) of white mice with spontaneous mammary carcinomas.

2. This is supported by the following circumstantial and direct histologic evidence:

(a) The distribution of megakaryocytes in the various organs precludes their exclusively embolic origin from the bone marrow.

(b) The absence or relative rarity of traumatized megakaryocytes in the spleen, liver and lymph nodes refutes the assumption that these cells have been carried to these organs by way of the blood-vessels.

(c) The relations existing between the frequency and distribution of heterotopic megakaryocytes and of extramedullary myeloid foci support the probability of the local origin of heterotopic giant cells.

(d) Proliferation foci in the form of megakaryocytic clusters in the spleen and transitional cell forms between reticulum and reticuloendothelial cells and megakaryocytes in the spleen, lymph nodes and liver point to the local genesis of these cells.

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LEUKOCYTOSIS AFTER PARENTERAL INJECTION OF LIVER EXTRACT.*

BY OVID O. MEYER, M.D.,

WILLIAM S. MIDDLETON, M.D.,

AND

ETHEL M. THEWLIS,

MADISON, WIS.

(From the Department of Medicine, University of Wisconsin.)

ORAL ingestion of whole liver is known to produce an increase in the leukocytes of the blood as well as other formed elements in patients with pernicious anemia (Murphy, Monroe and Fitz¹ and Minot and Murphy²). Murphy³ noted that a sharp increase in the leukocyte count follows within a few hours, intravenous or intramuscular injection of liver extract in patients with pernicious anemia. Recently Powers, Murphy and Humphreys⁴ found that a leukocytosis could also be produced in normal individuals by the injection of concentrated liver extract (Lederle). This leukocytosis, which was usually maximal in 6 or 7 hrs., was accompanied by an increase in neutrophils, both in total number and percentage. These workers suggest the possible value of parenteral liver extract in the treatment of some patients with persistent leukopenia and Foran, Sheaff and Trimmer⁵ have treated 5 patients

* This study supported in part by a grant from the Wisconsin Alumni Research Foundation.

suffering from malignant neutropenia by means of parenteral and oral liver extract with apparent good results.

It was deemed desirable to compare the leukocytosis produced by liver extract injected intravenously and intramuscularly both in normal and in abnormal individuals. Furthermore, it was hoped by this study that the origin of the leukocytosis might be elucidated. It is claimed that after epinephrin administration, the leukocyte increase is due to splenic contraction. If this were found to be the case after liver extract administration, its value therapeutically in this field would probably be much less and its use less logical than if the bone marrow were actually stimulated to increased production. A recent report of Miller and Rhoads,⁶ published as this work was being completed, suggests that this factor of splenic contraction is important. They noted increase in all formed elements of the blood, including the leukocytes, after the intravenous injection of liver extract, to a patient with anemia and splenomegaly. The increase in leukocytes, which is of primary interest here, was noted within 20 min. after the injection of the extract. Concurrent with this leukocytic increase, the spleen was observed fluoroscopically to be greatly contracted. Intramuscular injection of adrenalin gave results comparable to those with liver extract. A control patient without splenomegaly had no increase in the leukocytes or other formed elements in the blood stream under the same experimental conditions. Peculiarly, when eserin was injected intramuscularly in this same patient with splenomegaly, there was no peripheral increase in the formed elements of the blood although splenic contraction of a slower and lesser degree than with liver extract and adrenalin occurred.

Methods. In general, the methods of Powers, Murphy and Humphreys⁴ in their study on normal individuals have been followed save for slight modifications which will be noted in the description and graphs below.

Blood counts were made over 3-day periods. On the 1st and 3d days all counts were started at 9 A.M. and continued at 11 A.M. and 2 and 4 P.M. These days served as the control periods, while the 2d day was the experimental day in each instance. On this 2d day, blood was taken for a count at 8.55 A.M., the liver extract was injected at 9 A.M.; 20 min. later a 2d count was made, a 3d at 10 A.M. and then hourly until 7 P.M. Exceptionally a count was also made at 8 P.M.

Each count was done in duplicate,* using the same 2 pipettes and same hemacytometer throughout the 3 days of each individual experiment. (In 1 experiment 1 of the pipettes was broken, necessitating the use of another set of 2 for the remaining counts of that experiment.) Two counts were made from each pipette, *i. e.*, 1 on each side of the hemacytometer, the 4 large corner squares being counted each time. Thus, each count reported represents the average of 4 counts. Occasionally there was a wide variation in the counts from the 2 pipettes, but ordinarily not. The average discrepancy between the highest and lowest counts was 12%,

* Blood for each count was taken from a prick in the ear into standard 1 to 11 pipettes, diluted 1 to 20, shaken for 3 min. and counted at once in a Levy counting chamber. The pipettes and the counting chamber were certified by the U. S. Bureau of Standards.

with a range for individual experiments between 9 and 15%, the highest percentage error occurring in the patients with the lowest leukocyte counts.

Coverslip smears were stained with Wright's stain and the differential counts were made of 200 cells in each instance. Schilling counts were done on 2 or more of the smears of the control period before liver extract was given, and on 2 or more during the period of high leukocyte counts in each reported experiment in order to ascertain whether or not there was an increase in young neutrophil cells in the peripheral blood.

Concentrated liver extract (Lederle), in 3-cc. doses, was given in each experiment; but when administered intravenously it was diluted in normal saline to a volume of 15 cc. The intravenous injections were made during a period of 5 to 10 min. into a vein in the antecubital fossa and the blood pressure, which usually but not invariably fell moderately, was taken repeatedly during this procedure. Intramuscular injections were made into the buttock.

One of us served as a normal control, and in this case, usual activities were carried out during the 3-day experimental period. A 2d normal was a patient without demonstrable disease. Two others were recuperating from operations for inguinal hernia done more than a week before. They were, of course, afebrile and for the present purpose might be considered as normal. These 3 patients were kept in bed during the experiments but had their meals regularly. Temperature readings were made at 8, 12, 4 and 8 o'clock on these 3 subjects on the day of the liver injections and 8 and 4, or at the same 4 periods, during the control days.

Results. Observations on the normal individuals after the intramuscular injection of liver extract confirmed the results of Powers, Murphy and Humphreys. A typical result though not the most striking is shown in Fig. 1. For comparison, in this same figure is shown the leukocytosis produced by the intravenous administration of liver extract to this same subject 2 days before.

The sharper and more prompt but less well sustained rise in the number of leukocytes after the intravenous injection is obvious. This was a consistent observation in the 3 normal and 1 abnormal subjects that received the extract intravenously. The maximal leukocyte count was reached 3 hr. after the intravenous injection, whereas, when the extract was administered intramuscularly, the highest count was attained only 5 or more hours after the injection. The increase in the neutrophils paralleled the rise in total leukocytes and there was also a relative increase in neutrophils. This patient had temperature elevation to 99.4° F. in the afternoon both after intravenous and intramuscular injections, but no subjective or objective signs of a marked reaction. Only 1 of all the subjects had a distinct reaction with a moderately severe chill and a febrile reaction to 100.4° F., 1½ hr. after the extract was administered intravenously. His leukocyte count rose from an average control level of 9000 to 15,000.

In none of the normal individuals was there a demonstrable shift to the left in the Schilling counts.

Results in a Patient With Chronic Leukopenia. CASE 1.—The patient, G. C., a white woman, aged 30, had recovered from a severe neutropenia, with daily high fever, at times exceeding 104° F., and lasting more than

a week. The total white count had been as low as 250, with 9% neutrophils, and at one time with a count of 400 there had been 2% neutrophils. She had been treated with pentnucleotid during the acute stage of serious neutropenia; but at the time the liver extract was administered for this experiment she had received none for more than 3 weeks. The white count for more than a month before the experiment had been persistently low, usually ranging between 2000 and 5000, with a relative neutrophil count of 50% or more.

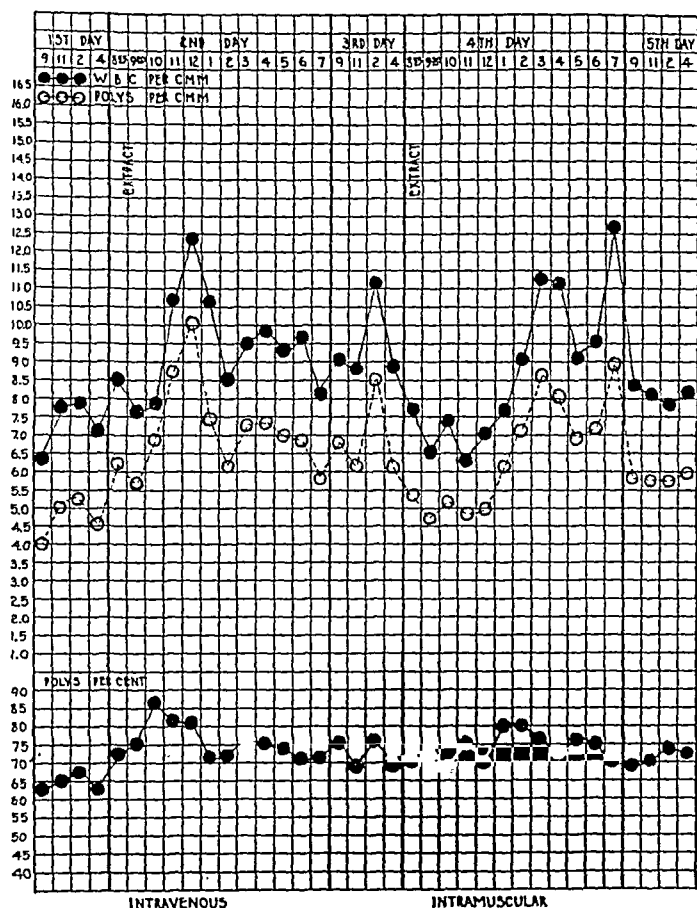


FIG. 1.—A comparison of the effect upon the leukocytes of intramuscular and intravenous administration of liver extract to a normal subject.

The experimental routine described above was followed; the liver extract (3 cc.) was administered intramuscularly at 9 A.M. on the 2d day. The patient was in bed throughout the period of the experiment. The result is shown in Fig. 2.

The response of the leukocytes resembles that of the normal shown in Fig. 1. A fall in the leukocyte count occurred 20 min. after the injection, followed by an increase above the basal level of the control periods. In this case the basal level is low and the maximum leukocyte count is not great; however, the actual level at 2 P.M., when the peak was attained, is 77% above the average of the control counts of the preceding day and 80% above the 2 P.M. count of the preceding day. An elevation in the total

and relative neutrophil counts is also similar to that of the normals. In this case, at 6 P.M. there was a second sharp rise of leukocytes to above 7000. This late rise was also observed at 7 P.M. in the experiment of Fig. 1 after the intramuscular injection of the extract. This 2d elevation of the leukocyte count was not a consistent finding, however, and no explanation for its occurrence is offered.

This experiment shows clearly that it is possible to elevate at least temporarily, a persistently low white count by injection of this

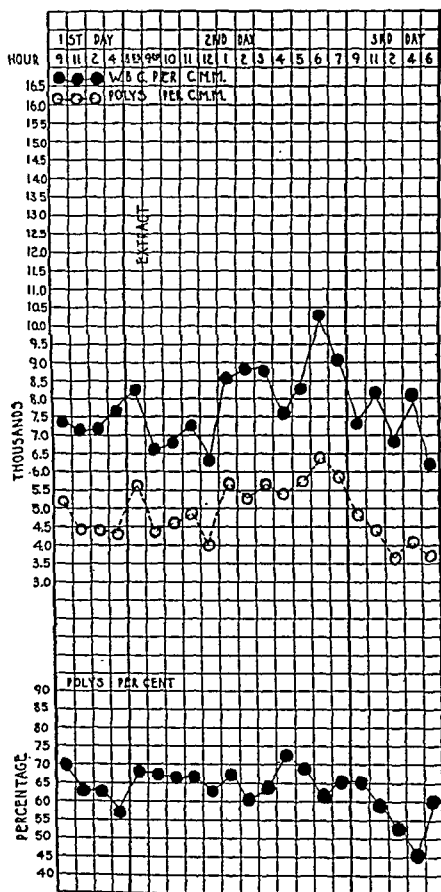


FIG. 2.—The effect of the intramuscular injection of liver extract upon the leukocyte count in a patient with a persistent leukopenia.

concentrated liver extract. Of course, this was observed on a single patient and a determination of the possible therapeutic efficacy of liver extract for this purpose requires further tests upon similar patients. Powers and his associates report that in their series one of the subjects developed influenza and with it a leukopenia during the period of observation. The response to the liver injected was nevertheless similar to that of the normal subjects in the temporary leukocytosis with total and percentage increase in neutrophils.

Effect of Liver Extract Before and After Splenectomy. CASE 2.—E. G., a well-developed, well-nourished white male, aged 38, was admitted to the hospital complaining of weakness. Save for marked pallor and a firm spleen, palpable 3 cm. below the costal margin, there was little of note on physical examination. Laboratory examinations on admission showed a hypochromic anemia, hemoglobin, 48% (Tallqvist), and red cells, 4,600,000, a persistent leukopenia with an approximately normal differential count. Fragility of the red cells was normal. Icterus index was 6; there was free acid in the aspirated gastric contents. Gastro-intestinal Roentgen rays revealed no abnormality. A diagnosis of Banti's disease was made and this was confirmed after operation by pathologic section and microscopic examination. Large doses of iron were administered, but liver was omitted. Shortly before the liver extract was given for the first experiment, the red cell count was 4,930,000 and the hemoglobin 55%.

Concentrated liver extract (3 cc. in 12 cc. of normal saline) was given at 9 A.M. There was some flushing of the face and increase in pulse rate during the injection and the systolic blood pressure rose from 130 to 146. Usually with intravenous injection of this extract a moderate fall in blood pressure occurred, but not in this instance. The leukocyte response to the injection was typical again with fall of the white cell count from 6700 at 8.55 A.M. to 4325 at 9.20 A.M. Subsequently there was an increase to a maximum of 8650 at 12 noon. This level was 40% higher than the average of the 4 counts (6150) of the day preceding the extract administration, and as the average of the 11 A.M. and 2 P.M. counts was 5450, the increase over the level for a similar period of the day was still greater. There was also an increase in the percentage of neutrophils.

The 3d day was a control period for this experiment and also the 1st control day for a 2d experiment, when liver extract was injected intramuscularly. The counts this day were lower than the day preceding the intravenous injection. The response to the intramuscular injection of liver extract is shown in Fig. 3. Here the early leukopenia usually observed was slight and delayed. The increase in total leukocytes from an average level of 4181 of the control day to 8312 at 3 P.M. (an increase of about 100%) and in the neutrophils is obvious. In this experiment, and in no other, the Schilling counts showed a significant shift to the left, the "stab" cells were increased from 4.5% before the intramuscular injection to 13.5% when the leukocytes were most numerous. In addition, at this latter period there were 3.5% metamyelocytes, whereas there had been none before.

Shortly after these experiments, a splenectomy was done. Three weeks after this operation, when the red cells numbered more than 5,000,000 and the hemoglobin was 70%, liver extract was again administered intramuscularly (Fig. 3). The basal level of the white cells was higher after splenectomy, and the response to liver extract more striking. The total count, when maximal, was 71% higher than the average of the control counts of the previous day. This experiment was repeated twice, once the 2d day after this reported experiment and then again 4 days after the 2d. As the results in these 2 experiments were quite similar, only the latter is shown in Fig. 4.

The leukocytosis here was slight as compared to the first experiment following splenectomy, but still evident. Interestingly, after showing a tendency to fall, high counts were recorded at 6 P.M., 9,300 and leukocytes 10,400 respectively, for these last 2 experiments. This patient was afebrile for days before and after each experiment, but at noon on the day of intravenous injection, the temperature was 99.6° F. and on the day of the intramuscular injection before splenectomy 99.2° F. at 4 P.M. The maximal temperature of the 3 experimental periods after splenectomy was 99.4° F., 99.2° F. and 99° F. on the respective days of the intramuscular injections.

CASE 3.—B. M., a white woman, aged 46, was admitted to the hospital because of weakness. Important findings on physical examination were pallor, icterus and an enlarged spleen, which extended 8 cm. below the costal margin or to below the umbilicus. Laboratory examinations on admission included a red cell count of 3,400,000—reticulocytes 16.7% and hemoglobin 62% (Tallqvist). The erythrocytes began to hemolyze in 0.67% salt solution. Gastric analysis showed the presence of free hydrochloric acid. A diagnosis of familial hemolytic icterus was made and a splenectomy was advised.

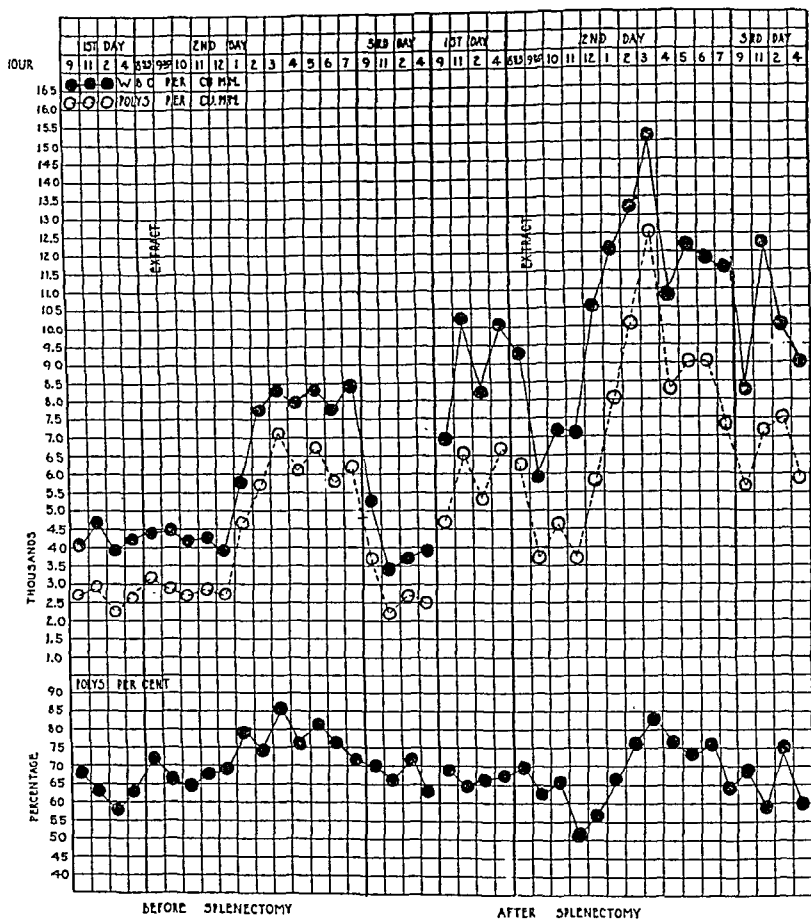


FIG. 3.—A comparison of the effect upon the leukocytes of the intramuscular administration of liver extract to patient (E. G.) with Banti's disease, before splenectomy and after splenectomy.

Before splenectomy, after the usual control period, liver extract (3 cc.) was administered intramuscularly and blood counts were done as in the other experiments. This study was repeated 17 days after splenectomy. The patient was kept in bed during both experimental periods until after the last count was done each day. Meals were taken at the regular hours, 7.30 to 7.45 A.M., 12 NOON and 5.45 to 6 P.M. The day of liver extract injection before splenectomy this patient's temperature was highest at 4 P.M., being 99.2° F. The day of the injection after splenectomy, the temperature was not above 98.6° F.

The effect of liver injection upon the white cell count before and after splenectomy is shown in Fig. 5. Because of continued rise in the white cell count before splenectomy until 7 P.M., an 8 o'clock count was made on the day of the injection, and a 6 o'clock count on the day after because of the 4 o'clock elevation on the control days.

Liver extract was again administered intramuscularly the 2d day after the postsplenectomy injection. Thus the 3d control period shown on Fig. 5 represented also the 1st control day for this 2d experiment. Again leuko-

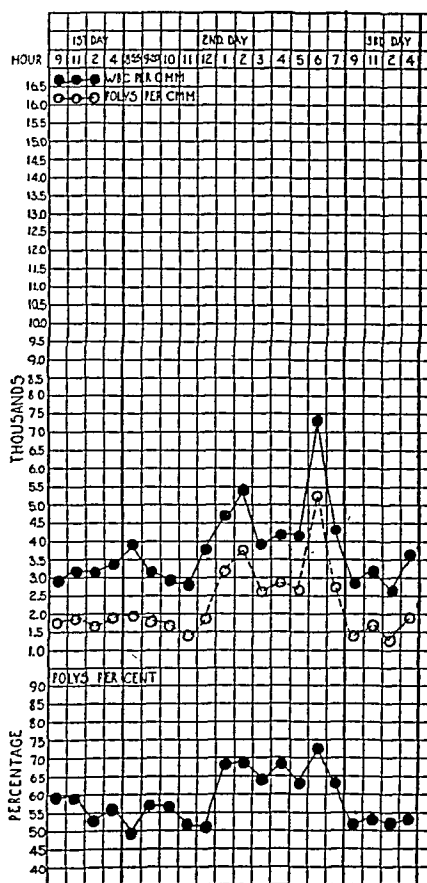


Fig. 4.—The effect of repetition of administration of liver extract to patient (E. G.), after splenectomy.

cytosis followed, reaching a height of 14,675 at 3 P.M., 6 hr. after the injection. The white cell count at 8.55 A.M., just before the extract was injected, was 8687. It should be noted that at the time of these experiments after splenectomy, the red cell count was 4,065,000 and the hemoglobin 80%. The fragility of the red cells was normal.

Particular attention is directed to the sharp fall in the number of leukocytes noted both before and after splenectomy when the count was taken 20 min. after the injection. In the experiment before splenectomy, the leukocyte rise commenced at about the usual time but the progression to a peak was slower than usual, the

summit not being attained until 7 P.M., 10 hr. after the injection. The percentage increase in neutrophils is more striking after splenectomy. Schilling counts both before and after splenectomy showed no increase in young cells over the normal numbers present before the injection of liver extract.

Discussion. These results, both for the normal and abnormal subjects, were quite pronounced and consistent. The trend of the leukocyte counts after the injection of this liver extract was similar

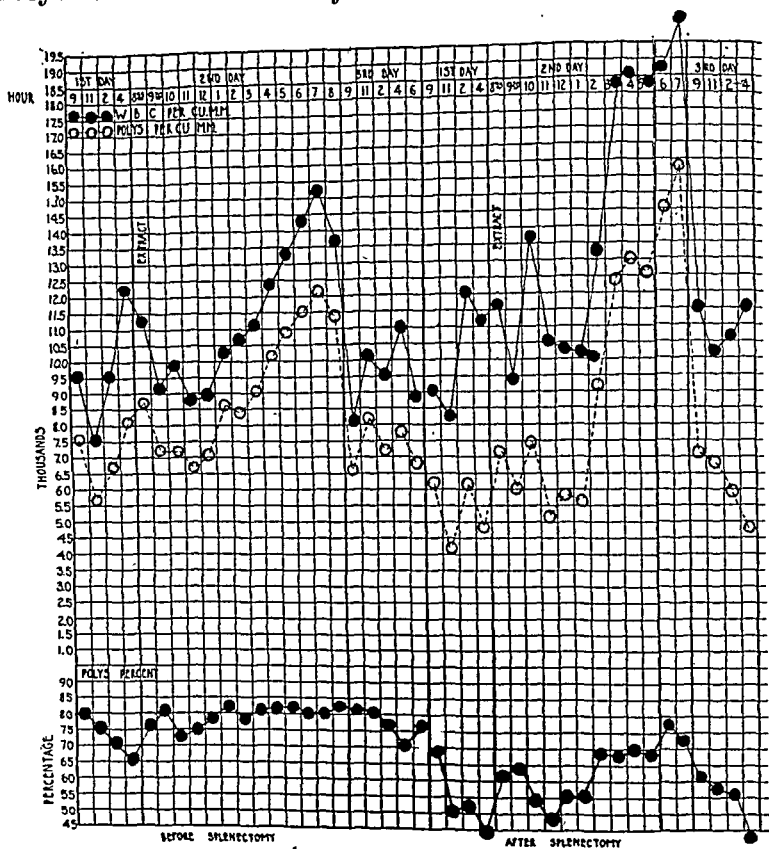


FIG. 5.—A comparison of the effect upon the leukocytes of intramuscular injections of liver extract in a patient with familial hemolytic icterus, before and after splenectomy.

in each case. The findings of Powers, Murphy and Humphreys⁴ were thus confirmed.

In each subject the conditions of activity, food intake and other extraneous factors were comparable during the 2 control days and the experimental day. Caution was exercised in this matter for it was appreciated that many factors might alter the leukocyte count appreciably. The administration of various drugs, particularly the injection of foreign proteins, will produce leukocytosis, although Murphy³ noted none after the intramuscular injection of aolan. Drug administration that might produce an increase in

leukocytes was avoided in the subjects under study, and Powers and his associates report that this liver extract (Lederle) has no foreign protein or infinitesimal amounts present. However, whether or not small amounts of protein exist is not of paramount importance in this investigation and no claim is made that leukocytosis cannot be produced by other methods.

In all of these experiments the liver extract was injected at 9 A. M., and thus when given intramuscularly, the maximum leukocytosis occurred in the middle or late afternoon. It was not thought necessary to administer it earlier so as to produce the leukocytosis earlier in the day, for when the extract was given intravenously, the maximum leukocytosis which was equal in degree occurred at 12 o'clock rather than at 3 or 4 P. M. Thus, the increase in leukocytes cannot be explained by a physiologic afternoon rise such as Shaw⁷ describes. Furthermore, Powers⁴ and his associates found that when the extract was injected intramuscularly at 5 A. M., instead of 9 A. M. the maximal response which was of similar degree occurred at 11 A. M. At this hour, according to Shaw,⁷ the leukocyte count is normally at a low ebb. In view of these experimental results, and because of care in excluding extraneous factors, it is our belief that the leukocytosis produced in these experiments was due to the injection of liver extract and was neither physiologic nor due to some agent other than the injected material.

The patient, E. G., with early Banti's disease and the patient with hemolytic icterus, B. M., had splenomegaly. The spleen was not very large in the first case, therefore this case will be ignored in the present discussion. However, in the case of B. M., the spleen measured approximately 22 by 13 by 9 cm. after removal and thus was probably comparable in size to the spleen in the case of Miller and Rhoads.⁶ The counts in their patients were done within 20 min. after the intravenous injection of liver extract, at which time there was an increase in the number of leukocytes as well as other formed elements of the blood. This early increase in white cells was not noted in our patient with splenomegaly nor in any other of the normal or abnormal individuals, whether the liver extract was given intravenously or intramuscularly. Instead, a decrease in the number of leukocytes was the usual rule 20 min. after the injection. This early decrease in leukocytes may possibly be explained by redistribution of the cells in the blood stream. The fact must not be overlooked that Miller and Rhoads used the liver extracts of other manufacturers than that which was used in this study. The results obtained after splenectomy in both E. G. and B. M. eliminate the possibility that the increase in leukocytes in the peripheral blood stream produced after the administration of this particular liver extract is due to splenic contraction. Furthermore, it very strongly suggests that the leukocytosis produced in the experiments on the normal individuals of the Powers, Murphy and Humphreys⁴

series and of this group was not due to splenic contraction. Consequently, it is possible that the effect may be due to actual stimulation of the bone marrow, directly or indirectly. Of course, the fact that splenectomy does not effect any change in the response to parenteral injections of liver extract does not rule out the possibility of hepatic or splanchnic responses which have been considered in this relation. The possibility of the existence of accessory spleens in both E. G. and B. M. is not overlooked although this is unlikely. Furthermore, it would seem improbable that an organ the size of the ordinary accessory spleen could produce significant changes in the leukocyte count.

In only one of the Schilling counts, in the case of E. G. before splenectomy, was there noted a demonstrable shift to the left. This was when liver extract was injected 2 days after a previous injection. However, it is possible to stimulate bone marrow with the production of leukocytosis of short duration without calling forth young neutrophils into the peripheral blood stream. That young cells did appear however in 1 case, after leukocytosis had been induced just 2 days before, adds further strength to the belief that the leukogenetic centers in the bone marrow were stimulated by the liver extract.

Since liver extract apparently stimulates bone marrow, force is added to the suggestion of Powers and his associates that it "might be utilized clinically in the treatment of patients with chronic sepsis and a persistently low level of leukocytes." Possibly it also lends a measure of support to the therapy of Foran, Sheaff and Trimmer,⁵ in agranulocytic angina. However, the etiologic factors and the status of the bone marrow in this disease demand further clarification before any positive statement can be made in this direction.

Summary and Conclusions. 1. The parenteral administration of concentrated liver extract (Lederle) was ordinarily attended by by an early fall in the white cell count and a constant subsequent leukocytosis with increases in total and relative numbers of neutrophils in 4 normal and 3 abnormal individuals.

2. The maximal leukocyte count was usually attained 3 hr. after the intravenous injection of the extract and 5 hr. or later after the intramuscular injection. After the intramuscular injection the rise, though less prompt, was better sustained.

3. In a patient with chronic leukopenia there was an increase in leukocytes to a maximum of 73% above the control period level.

4. In a patient with Banti's disease with leukopenia, leukocytosis was produced repeatedly by the parenteral injection of liver extract both before and after splenectomy. Also, a shift to the left in the Schilling count occurred on the occasion of an intramuscular injection before splenectomy. This was 2 days after the intravenous administration of the same extract.

5. Leukocytosis also occurred before and after splenectomy in a patient with familial hemolytic icterus.

6. Since leukocytosis can be produced by the intramuscular injection of this concentrated liver extract after splenectomy, it would appear that this substance does not produce the increase in the leukocytes by inducing splenic contraction, but possibly by a stimulation of the bone marrow, directly or indirectly.

7. The administration of liver extract to induce an elevation in the white count, at least temporarily, is logical. Its efficacy and limitations will be established by a thorough clinical trial.

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SURGICAL ASPECTS OF PERNICIOUS ANEMIA WITH SPECIAL REFERENCE TO THE TREATMENT.

By R. G. HAHN, M.D.,

RESIDENT PHYSICIAN, PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

(From the Medical Clinic of the Peter Bent Brigham Hospital, and the Department of Medicine of the Harvard Medical School.)

IN 1924 Minot and Murphy developed their well-known treatment for pernicious anemia.¹ Adequate treatment may be defined as that amount of liver which induces a remission and maintains the patient in the best condition of health.^{4,6,10} Whether the treatment is carried out by the oral,⁴ intramuscular⁷ or intravenous³ administration of potent liver preparations from this point of view is of no consequence. Intravenous injections, however, do not yet possess the security that is present in the other methods.

It is well recognized that certain conditions such as undue fatigue, inadequate nutrition and mental anxiety⁶ can delay and prevent the restoration of a normal red blood cell picture, even though adequate treatment apparently is given to the patient. The most important hindrances in the development and maintenance of a normal blood picture in a patient with pernicious anemia are blood loss and infection.^{5,8} The surgical procedure sometimes necessary to eradicate these hindrances may be a major or a minor operation. The influence of these inhibitory factors and the rather frequent need for surgical intervention led us to review the cases of pernicious

anemia that had been operated upon at this hospital and ascertain how they tolerated the operation, the effect of the operation on the blood picture, and the subsequent condition of the patient.

Prior to 1925 (pre-liver treatment era) 8 cases of pernicious anemia were operated upon. Table 1 presents a brief tabulation of the particular phases of these cases with which this report is concerned.

TABLE 1.—HEMOGLOBIN AND RED BLOOD CELL COUNTS BEFORE AND AFTER OPERATION.

	Age.	Before operation.		Days after operation.	After operation.	
		Hb. %.	R. B. C. in millions.		Hb. %.	R. B. C. in millions.
Limits	32-59	50-75	1.07 to 3.36	1-15	25-65	1.00 to 2.61
Average	48	60	1.99	6	50	1.64

These 8 cases (4 males, 4 females) had a total of 9 operations: 2 splenectomies, 1 nephrectomy, 1 trephine of tibia and rib, 1 reamputation of leg, 1 cholecystectomy, 1 cholecystectomy and splenectomy, 1 repair of traumatic laceration of hand, wrist and neck, 1 rib resection for drainage of empyema. Before the operation, 5 cases had a red blood cell count less than 2,000,000 cells per cmm. The remaining cases had 2,000,000 erythrocytes per cmm. or more. After the operation 7 cases had a red blood cell count less than 2,000,000 cells per cmm.; the remainder were above 2,000,000. Ether anesthesia was used on 4 occasions, gas-oxygen twice and novocain 3 times. The average time for the operation was 1 hr.; the limits 20 min. to 2 hr. and 15 min. Four blood transfusions were given to 3 patients before the operation and 8 transfusions to 5 patients after the operation. The average amount of each transfusion was 450 cc. Three of the 5 patients that were transfused after the operation had been transfused before the operation. There were no striking changes in any of the red blood cell counts. One patient died 20 days after a cholecystectomy and another 40 days after repair of traumatic lacerations of hand, wrist, and neck. Five patients died 1 to 3 years after the operation in a relapse of their pernicious anemia. One patient could not be traced.

The number of these cases is small. No definite conclusions can be drawn from them, but they do furnish some information which can be compared with that obtained from those who came fortunately at the time designated as the liver treatment era. The following table, similar in outline to the first one, presents a tabulation of those cases that received liver.

TABLE 2.—HEMOGLOBIN AND RED BLOOD CELL COUNTS BEFORE AND AFTER OPERATION.

	Age.	Before operation.		Days after operation.	After operation.	
		Hb. %.	R. B. C. in millions.		Hb. %.	R. B. C. in millions.
Limits	32-70	60-106	2.75 to 5.74	1-15	50-95	3.25 to 5.26
Average	55	76	4.20	6	70	4.10

These 24 patients (14 males, 10 females) had a total of 31 operations. Before 8 of these operations the red blood cell count was less than 4,000,000 cells per cmm., in the remainder it was more than 4,000,000. After the operation 11 cases had less than 4,000,000 red blood cells per cmm., and the remainder had more than 4,000,000. The following table records the operation, the type of anesthesia used, the time interval since the operation and the patient's condition at that time.

TABLE 3.—RÉSUMÉ OF OPERATIONS AND FOLLOW-UP OF PATIENT.

Case No.	Operation.	Anesthetic.	Follow-up.	Condition.
1.	Hemorrhoidectomy	Ether	7 years	Good.
	Dilatation and curettage and radium implantation	Ether	6 years	Good.
2.	Explore chest abscess	Novocain		
	Resect 3 costal cartilages	Novocain	7 years	Good.
3.	Appendectomy	Ether	6 years	Good.
4.	Amputation of breast	Gas-oxygen	5 years	Good.
5.	Cholecholestomy	Ether	4 years	Good.
6.	Herniorrhaphy	Spinal	3 years	Good.
7.	Facial repair of hernial scar	Spinal	3 years	Good.
8.	Hemorrhoidectomy	Spinal	2 years	Good.
9.	Herniorrhaphy	Novocain	2 years	Good.
10.	Hemorrhoidectomy and radical antrum	Spinal	2 years	Died 2 months after a cholecystectomy.
		Cocain		
11.	Cervical amputation	Ether	2 years	Good.
	Apical abscess drained	Gas-oxygen	6 months	Good.
12.	Hydrocele excision	Spinal		
	Hemorrhoidectomy	Spinal	2 years	Good.
13.	Hemorrhoidectomy	Spinal	1 year	Good.
	Cervical amputation with ant. and post. colporrhaphy	Spinal		
14.	Cholecystectomy	Avertin	1 year	Fair.
15.	Hemorrhoidectomy	Spinal	1 year	Good.
16.	Excision carbuncle	Gas-oxygen	1 year	Good.
17.	Hysterectomy and removal of adnexa	Avertin	1 year	Good.
18.	Hemorrhoidectomy	Novocain	1 year	Good.
19.	Dilatation and curettage and radium implantation	Gas-oxygen	6 months	Good.
20.	Cholecystectomy	Avertin	5 months	Dead.
21.	Cholecystectomy	Gas-oxygen	4 months	Dead.
22.	Hemorrhoidectomy	Ether	3 months	Good.
23.	Hydrocele excision	Spinal		
	Suprapubic prostatectomy	Spinal	3 months	Fair.
24.	Resection of part of colon for carcinoma	Ether	3 months	Good.

Spinal anesthesia was used 11 times, ether 7, gas-oxygen 5, novocain 4, avertin 3 and cocain once. In isolated instances the novocain and avertin were reënforced with gas-oxygen and ether respectively. The average time of the operations was 1 hr. (10 min. and 4 hr. extremes). Whenever possible the operation was deferred until the patient's red blood cell count was within normal range. There were no deaths in this group that could be attributed directly to the operation.

Case Abstracts. CASE 10.—A man, aged 54, was operated upon for hemorrhoids and an infected left antrum. His blood picture was essentially normal both before and after the operations. He had been maintained on 4 ounces of liver pulp or 2 to 3 vials of liver extract daily for several months previously and this same régime was continued throughout his operations and postoperative periods. Two years after discharge he had a cholecystectomy. Neurological symptoms, that were already present, increased markedly. He developed a phlebitis and died from a cerebral embolus 2 months after the operation. An autopsy did not throw much additional light on his case except to confirm the diagnosis of pernicious anemia.

CASE 21.—A male, aged 55, died 4 months after a cholecystectomy. Before the operation his blood showed a hemoglobin of 80% and an erythrocyte count of 4,220,000 cells per cmm. For more than a year he had been maintained on raw and cooked liver, and for the last few months on 2 to 3 vials of liver extract daily by mouth. During this time his red blood cell count remained about the same as that stated above. His immediate post-operative course was stormy, complicated by "shock" and marked weakness. The latter persisted for more than 2 weeks and his anemia progressed. On the 23d day after the operation his red blood cell count was 2,700,000 cells per cmm. This developed despite the intake of 4 vials daily of a known potent liver extract, which was started on the 4th postoperative day and 2 days later increased to 6 vials daily. At the time of discharge from the hospital (81 days after the operation) he had a red blood cell count of 4,230,000 cells per cmm. and a hemoglobin of 80%. The cause of his death was not ascertained.

CASE 20.—A 56-year-old female, who responded well to liver extract given orally, had a relapse under treatment and developed neurological symptoms. An intravenous cholecystogram showed a non-functioning gall bladder. Following a cholecystectomy she had an uneventful convalescence; her red blood cell counts improved moderately. She continued her liver medication and was readmitted 4 months later. A trophic ulcer had become infected and she died 6 weeks after admission, 5 months after the cholecystectomy. A postmortem examination showed extensive thrombosis of the iliac veins and lateral sinuses apparently related directly to the infected trophic ulcer.*

In this group liver treatment was resumed on an average of 2 days after the operation. Twenty cases received liver preparations orally and 11 intramuscularly. Raw liver pulp and (Lilly's) liver extract No. 343 (N. N. R.) were the preparations given orally. Nine cases received the former, 9 the latter, and 2 were given both preparations. They received 250 to 600 gm. of the liver pulp or the equivalent value of liver extract daily. Eleven cases were treated exclusively by Lederle's intramuscular liver extract, receiving 3 to 6 cc. daily for 1 to 3 days depending on the severity of their anemia and subsequently 3 cc. once a week until discharged.

Blood transfusion was used twice in this group of cases.

CASE 14.—A 65-year-old woman had responded poorly to liver therapy. Her red blood cell count had not increased more than 500,000 cells per cmm. in 4 weeks. She had received 3 intramuscular injections of liver extract in the first 2 weeks and 6 vials of liver extract daily by mouth during the last 2 weeks. While on the ward she developed an acute exacerbation of a chronic cholecystitis. The day before the operation her blood showed a hemoglobin of 65% and an erythrocyte count of 2,750,000 cells per cmm. She was given a transfusion of 300 cc. of blood and a cholecystectomy performed under avertin anesthesia. On the 7th day after the operation she was started on 6 vials of liver extract daily by mouth. Her entire post-operative course was uneventful. Blood examinations on the 10th day after the operation showed a hemoglobin of 55%, red blood cell count of 3,456,000 cells per cmm., and on the 35th day 65% and 4,290,000 respectively. At present, 1 year after the operation, she is in fair condition and has taken liver irregularly.

* The reference is a complete report of this case.

The following case illustrates some contingencies that may develop when the patient is not treated adequately before and after an operation.

CASE 23.—A 70-year-old man had had symptoms of pernicious anemia for more than 8 years. He received adequate treatment and during the past year had been kept in good health and maintained a normal red blood cell count on one intramuscular injection of liver extract every 6 weeks. Two weeks after one of his injections he was operated upon for a hydrocele sac and an enlarged prostate gland. His normal blood counts seemed to be a sufficient indication to the surgeons that no treatment was needed for his pernicious anemia until the usual time for his next injection. Two days after his second operation his red blood cell count was 2,920,000 cells per cmm. Intensive treatment was instituted with amelioration of his weakness and anorexia. He developed marked ataxia and paresthesia of his hands and legs. Twelve cc. of liver extract were given intramuscularly during the next 3 days, and one injection of 3 cc. each week thereafter. Three months after the operation his red blood cell count was 4,750,000 cells per cmm., and his neurologic symptoms had improved moderately.

A total of 10 oral operations were performed in both these groups, dealing only with the removal of several teeth, root fragments, or both. None of the patients had any unusual reactions. The operations were done under gas-oxygen anesthesia or local novocain injections. None of these patients had erythrocyte counts below 3,000,000 cells per cmm. before the operation. Complete blood studies after the operation were lacking in most instances.

It is interesting to note that 12 of the 24 patients in the second group had had 27 operations previous to those indicated in Table 3. Of these operations, 21 were done prior to the liver treatment era. Of the 27 operations, 15 were major procedures (appendectomy, cholecystectomy, hysterectomy, salpingectomy, herniorrhaphy).

Discussion. Previous to the advent of liver therapy the treatment of pernicious anemia patients before and after operation consisted largely of blood transfusions. The tendency to spontaneous remissions made it extremely hazardous for any prophet except Father Time to evaluate the efficiency of a given method of treatment. Certainly the advantages of splenectomy have not become apparent and can hardly be considered as an adjunct in the treatment of this disease.² The advent of liver in the treatment has changed this aspect of the problem completely, and the utility of the various preparations now employed enables one to treat the patient adequately throughout the operative period. Intramuscular injections of liver extract have largely replaced at this hospital the oral preparations. The injections cause only slight discomfort and only minor reactions have been encountered.

In the first group of cases reported (those before the advent of liver therapy) many blood transfusions were used: in the second group (those after advent of liver therapy) only 2 transfusions were thought to be necessary. In the first group 5 patients died within 3

years after discharge from the hospital, and 2 died 20 and 40 days after the operation. In only 1 of these 8 patients could the operation be said to have been related directly to the mortality, and in this instance a complicating cardiac and renal insufficiency was the main cause of the death. These cases tolerated the operations very well. Their average erythrocyte counts were low and the slight reduction of the red blood cell count after the operation was enough to aggravate the existing anemia. Their postoperative course was no more subject to complications than that of similar cases without pernicious anemia. The numerous transfusions doubtless played a major rôle in aiding these patients to tolerate the operations so well.

In the second group the operations were deferred, if possible, until the red blood cell count was within normal range. If immediate surgical intervention was indicated, the operation was performed and the patient received intensive liver therapy, abetted by transfusion if necessary. Case 14, cited previously, was the only one in this group operated upon when the red blood cell count was low. If the hematologic response was unsatisfactory and a condition amenable to surgical treatment existed, operation was advised and carried out when the patient was in the best condition possible. Cases 1, 2 and 8 are examples of this situation. Adequate treatment over quite a long period did not bring their red blood cell counts entirely to normal. After the operation a normal erythrocyte count was established and maintained. A brief history of these cases follows.

CASE 1.—A 42-year-old woman had had symptoms of pernicious anemia for 2 years. She responded well to treatment. Her erythrocyte count varied from 3.5 to 4.5 million per cmm. She had intermittently bleeding hemorrhoids and moderate menopausal bleeding. Since the operation her erythrocyte count has been consistently over 5 million. The treatment of her pernicious anemia has been the same since operation as it was previously.

CASE 2.—A 63-year-old man was under treatment for a year for pernicious anemia. He made a good initial response but his red blood cell count remained in the vicinity of 3.5 million. He was operated upon for a tuberculous abscess of the chest wall. Within 2 months his count had risen to 4.5 million and has remained between that level and 5.5 million on practically the same amount of liver as he had taken before operation.

CASE 8.—This man of 52 years had had symptoms of pernicious anemia for 2 months and responded well to treatment. He had intermittent bleeding hemorrhoids. Previous to operation his red blood cell count had averaged 4.5 million, decreasing to 3.5 million when he lost blood. After operation his red blood cell count reached and maintained consistently more than 5 million on the same, or equivalent, liver therapy as he had taken previously.

It is interesting to note the 3 mortalities. They had had cholecystectomies, 2 of which (Cases 20 and 21) were done in this hospital. The former has been presented. The latter did not improve and died 4 months after the operation with well advanced neurologic

changes. The 3d one (Case 10) was operated upon in another hospital and died 2 months after the operation. These 3 incidents cannot help but bring to mind the possible relationship between biliary and hepatic disease and anemia, particularly pernicious anemia.^{11,12} The postoperative course in these 3 patients was uncomplicated in 1, "stormy" in another, and that of the 3d is not known. All 3 had moderate subjective neurologic symptoms, and in 2 of them these symptoms became progressively worse. In contrast to these, Case 14, one year after a cholecystectomy, had a red blood cell count of 3,500,000 cells per cmm. She did not feel well but had not followed her liver treatment faithfully.

Whether or not these deaths have any relation to the operation, the condition of the patient previous to the operation, or the method of treatment, we are not prepared to state. Satisfactory information has not been obtained of the treatment and clinical course either of Case 10 that had a cholecystectomy in another hospital, or of Case 21 that died after discharge from this hospital. It does not appear likely that the operation can be blamed or criticized. As far as can be determined there were no unusual differences in the general physical condition of these 3 patients and others who had operative procedures of equal magnitude.

In this review the presence or absence of neurologic symptoms was noted before and after operation. Exact information frequently was not given. Whenever it was noted these symptoms were practically always made worse by the operation and several times made their initial appearance soon after the operation. This was especially apt to occur when adequate treatment was not provided, or when a marked fall in the red blood cell count followed the operation (see Case 23 cited previously). Improvement in the red blood cell count is frequently, though not always, accompanied by a diminution in the neurologic symptoms. Although the cause of these central nervous system changes is not known, it is reasonable to assume that the anemia does not play a neutral or disinterested rôle. Possibly forced confinement in bed after surgical treatment may play some causative part.

Whether the liver was given intramuscularly or by oral administration did not appear to make any difference, provided an adequate amount was taken by the patient. The advantages of the intramuscular route are obvious. By this method a definite amount can be administered, and the treatment can be carried out regardless of the nature of the operation and of the type of anesthesia employed. The essential feature is to give an adequate amount of potent material.

Most of these patients were given iron (ferrous carbonate [U. S. P.] or ferric and ammonium citrate [U. S. P.] 3 to 6 gm. daily), usually being begun in the convalescent period. The red blood cell counts were made 1 to 12 days before the operation (average 3 days).

Those recorded after the operation were done at 1 to 15 days (average 6 days).

These patients with pernicious anemia tolerate operative procedures very well. They do not seem to be subject to surgical complications any more than other patients. The type of anesthetic employed and the length of time that the operation required did not bear any relation to the complications or the end results. The definite impression that following an operation central nervous system symptoms may develop or be increased, if already present, certainly should be taken into consideration when the operation is not strictly necessary. The erythrocyte count tends to decrease after the operation, which apparently is not a result of blood loss. This can be greatly lessened and frequently obviated if treatment is given intensively before the operation and continued through convalescence. Sources of blood loss and infection frequently stand as barriers successfully preventing the attainment or maintenance of normal red blood cell levels. In those instances the eradication of these foci has a distinct therapeutic value and should not be neglected. The possible development of cord changes demands the fullest safeguard that can be provided, and at present this is intensive treatment during the pre-operative and postoperative periods.

Summary and Conclusions. A series of 32 cases of pernicious anemia that were operated upon is presented, with a discussion of the influence of the operation on their pernicious anemia and on the possibility of the development of central nervous system lesions. Many of these patients had sources of blood loss or infection which seemed to prevent the establishment or maintenance of normal red blood cell counts. The removal of these sources appeared to have a definite therapeutic value, as subsequent red blood cell counts showed an increase in the number of erythrocytes. Most of the cases received intensive treatment before the operation and during the postoperative period. One exception developed marked symptoms of central nervous system damage following the operation. It is our strong impression that surgical operations on patients with pernicious anemia have a definite tendency to precipitate or increase the development of neurologic symptoms. These can and should be guarded against by intensive liver therapy before and after operation.

Patients with pernicious anemia that are treated intensively before the operation and during the postoperative period tolerate surgical operations very well and are good surgical risks.

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THE RELATION BETWEEN ORAL AND RECTAL TEMPERATURES IN NORMAL AND SCHIZOPHRENIC SUBJECTS.*

BY HUGH T. CARMICHAEL, M.D., C.M., M.S.,

CLINICAL RESEARCH PSYCHIATRIST, RESEARCH SERVICE,

AND

FORREST E. LINDER, PH.D.,

ASSOCIATE STATISTICIAN, RESEARCH SERVICE, WORCESTER STATE HOSPITAL,
WORCESTER, MASS.

WITH THE COLLABORATION OF THE RESEARCH STAFF OF THE WORCESTER
STATE HOSPITAL.

(From the Worcester State Hospital and the Memorial Foundation for Neuro-
endocrine Research, Harvard Medical School.)

BODY temperature in man has been studied intensively since the latter half of the 19th century. Historical reviews have been presented by Wunderlich,¹ Pembrey² and by Woodhead and Varrier-Jones.³ These deal with the development of thermometry in medicine, the introduction of the clinical thermometer, and the general acceptance by the medical profession of the value of a knowledge of body temperature in the diagnosis and treatment of disease. Wunderlich's classical work¹ played a major rôle in emphasizing the importance of studying body temperature.

Many investigations have been directed toward ascertaining the temperature in various parts of the body and the relations among these. Numerous studies have been made of the influence of such factors as exercise, food, sleep, climate, age, sex, disease, etc., on heat regulation. Reference to a large number of these may be found in the reviews noted above.

Several parts of the body are used in the determination of temperature. The axilla is generally so utilized in Europe and Great Britain. In this country the mouth is preferred. The rectum commonly serves as the site when temperature measurements are made in infants and children; but in recent years, clinicians have more and more frequently selected the rectum as the location in both adults and children.

* Submitted by Dr. R. G. Hoskins, Director of Research, The Memorial Foundation for Neuro-endocrine Research.

Physiologic and clinical researches frequently involve the determination of body temperature. Sometimes the results of oral measurements are reported; at other times rectal measurements. In dealing with psychotic subjects it is often necessary to make rectal rather than oral measurements because of uncoöperativeness. This causes difficulty when attempting to compare results with published reports in which oral temperature was measured.

There appears to have become widespread in this country among members of the medical profession and nurses the impression that the rectal temperature exceeds the oral by 1° F. Just how this has come about is difficult to explain. Numerous observers have pointed out that the difference between the temperature in the mouth and in the rectum may vary from 0° F to 2° F, or even more if taken immediately after exercise or in cold weather. Burton-Fanning and Champion⁴ state that the rectal temperature is on the average 0.4° F higher than the oral and give the limits of variation as 0.0° F to 0.8° F. Wunderlich¹ notes the rectal temperature as 0.5° F to 2° F (on the average 0.7° F) higher than that in the mouth. Pembrey⁷ gives the average difference between oral and rectal temperature, obtained from the results of several observers, as 0.72° . Bardswell and Chapman⁶ give 0.9° at rest and 1.8° immediately after exercise as the difference. Reichert⁷ says the mean rectal temperature is 0.18° to 1.8° higher than the mean oral temperature. Hewlett⁸ states the difference as one degree and notes that this figure is increased when the mouth has been cooled. Burton-Opitz⁹ gives the difference as 0.54° . Howell¹⁰ apparently follows Pembrey² in giving the average oral temperature as 98.36° and the average rectal temperature as 98.96° . Macleod¹¹ says that the rectal temperature is usually about 1.8° higher than the oral. Wright¹² states that the rectal temperature is 0.50° to 0.75° higher than the oral and that it may be higher after exercise. It is clear that the general acceptance by physicians of one degree as the standard difference does not take proper account of the literature.

In many instances in clinical work no harm may be done by accepting 1° F as the standard difference. But in certain research problems it is necessary to know the nature of the relation of the two variables. It has seemed desirable, therefore, to investigate oral and rectal temperatures in order to determine more accurately the relationship between them. Along with investigation of this relationship, some points of general clinical importance and interest have been studied. The two groups of subjects used in the study enable a comparison to be made between normal subjects and those suffering from schizophrenia. In addition, observations on so-called "normal" body temperature have been made.

Methods and Materials. Simultaneous readings of oral and rectal temperatures were made in 25 hospitalized male schizophrenic subjects and in 24 normal male subjects, during December, 1932, and January, 1933.

For each subject readings were taken twice a day (for 12 nearly consecutive days), one between 8 and 9 A.M. and one between 4 and 5 P.M. This gave 24 pairs of simultaneous determinations for each subject. A total of 2352 observations were made.

The schizophrenic group ranged in age from approximately 17 to 45 years and was free from any detectable physical disease or deformities. The normal group consisted of apparently healthy physicians, research workers, and attendants, ranging in age from approximately 21 to 45 years. The degree of activity differed somewhat in the two groups. The patients were less active, were confined to the wards throughout the course of the study, followed a more regular routine of daily life, and rested $\frac{1}{2}$ to 1 hr. before each reading was made. The "normals" were more active, many lived on the hospital grounds apart from the main buildings, none followed a regular daily routine, and immediately preceding the temperature readings they rested not at all, or only for a few minutes.

Before the experiment was begun the clinical thermometers, graduated in degrees Fahrenheit, were immersed simultaneously in water, the temperature of which was determined by a standard scientific thermometer. The average thermometer reading was computed for each of 12 tests and the discrepancy of each thermometer from this average tabulated. The greatest average discrepancy was 0.07° . The thermometers were paired on the basis of the average discrepancy so that 6 practically equivalent pairs were obtained. One pair was assigned to each subject. Therefore, all oral readings on any one subject were taken with a single thermometer and all rectal readings on that subject were taken with a matched thermometer.

All observations were made in well-heated rooms, with the subjects recumbent and fully clothed except for the time necessary to permit insertion of the thermometer in the rectum. The morning readings were made within an hour after breakfast and the afternoon readings within an hour before supper. For both oral and rectal readings the thermometers were in place for at least 10 min. In all instances care was taken to have the thermometers correctly placed in the mouth and inserted at least 5 cm. in the rectum. In the schizophrenic subjects it was necessary to keep constant watch to insure that the lips were tightly closed and that there was no manipulation of the thermometer with the tongue. If these requirements were not strictly fulfilled the time the thermometers were in place was extended—in some instances to as long as 20 min. Generally the coöperation was such that a reliable measurement could be made in minimum time.

Results and Discussion. For each subject the measurements of oral temperatures made in the morning and afternoon are grouped together (Table 1). The rectal readings are similarly grouped. An objection might be raised to this procedure as ignoring the diurnal variation in body temperature. However, as shown by Table 2, the difference between the mean oral as well as the mean rectal temperatures of morning and afternoon for schizophrenic subjects is only 0.14° . For "normals" these differences are 0.29° and 0.10° , respectively.

In contrast with these relatively minor differences are the results obtained in a supplementary study at a longer interval between readings. At 4 to 5 A.M. and 4 to 5 P.M. measurements were made on 61 schizophrenic subjects every day for 30 days; a second period of 30 days followed 2 months later; and a final 30-day period after

another 2 months⁵. Most of the patients used in the smaller group served also for the latter study. The average differences between the morning and afternoon readings for the 3 periods were 1.32°, 1.36°, and 1.32° (Table 3). These differences are large in comparison with those noted between the 8 to 9 A.M. and 4 to 5 P.M. readings.

TABLE 1.—AVERAGE ORAL AND RECTAL TEMPERATURES FOR "NORMALS" AND SCHIZOPHRENICS.

Individual means—"normals."	No.	Min.	Max.	Range.	Mean and standard error.
Oral	24	97.4	98.4	1.0	97.93 \pm 0.06
Rectal	24	98.2	99.5	1.3	98.88 \pm 0.07
Individual means—"Schizophrenics."					
Oral	25	97.6	98.8	1.2	98.25 \pm 0.06
Rectal	25	98.2	99.5	1.3	98.79 \pm 0.06
Mean differences—"normals"	24	0.42	1.79	1.37	0.95 \pm 0.07
Mean differences—"Schizophrenics"	25	0.26	0.80	0.54	0.54 \pm 0.03

TABLE 2.—MEAN MORNING AND AFTERNOON TEMPERATURES FOR "NORMALS" AND SCHIZOPHRENICS.

Standard Errors are Used.

	A.M.	Oral.	P.M.	A.M.	Rectal.	P.M.
Patients	98.17 \pm 0.06		98.31 \pm 0.06	98.72 \pm 0.07		98.86 \pm 0.06
Controls	97.80 \pm 0.07		98.09 \pm 0.06	98.81 \pm 0.10		98.91 \pm 0.08

TABLE 3.—AVERAGE MORNING AND AFTERNOON RECTAL TEMPERATURES FOR PERIODS OF 1 MONTH EACH IN 61 SCHIZOPHRENIC PATIENTS.

Standard Errors are Used.

	4 to 5 A.M.	4 to 5 P.M.	Difference.
I Period	97.5 \pm 0.02	98.8 \pm 0.03	1.32 \pm 0.04
II Period	97.6 \pm 0.03	99.0 \pm 0.02	1.36 \pm 0.03
III Period	97.7 \pm 0.04	99.1 \pm 0.03	1.32 \pm 0.04

The mean difference of 0.95° between oral and rectal temperatures in the normal subjects would at first glance seem to bear out the impression of clinicians that the rectal temperature is about 1° higher than the oral. But it must be remembered that this is the average difference for the entire group; the average difference in individuals of the group ranged from 1.79° to 0.42°. The difference between oral and rectal measurements at any one time showed even more marked variation than the mean differences. In one normal subject the rectal temperature was 3.5° higher than the oral; in another the oral was 1.7° higher than the rectal. The graph in Fig. 1 indicates clearly how widely scattered are the differences in individuals and shows that even the bulk of the observations represents a wide range. It is obvious that the use of the mean difference of 0.95° as the standard by which to estimate the relationship of oral to rectal temperature of any given individual case is entirely unreliable.

In the schizophrenic group the mean difference is 0.54°. The average difference in individuals of this group ranged from 0.80° to

0.26°. In one subject on one occasion the rectal temperature was 1.8° higher than the oral; in another the oral reading was 0.6° higher than the rectal. The graph, Fig. 2, illustrates these findings.

Comparison of the figures obtained for the schizophrenics with the figures for the normal group reveals distinct differences. It has

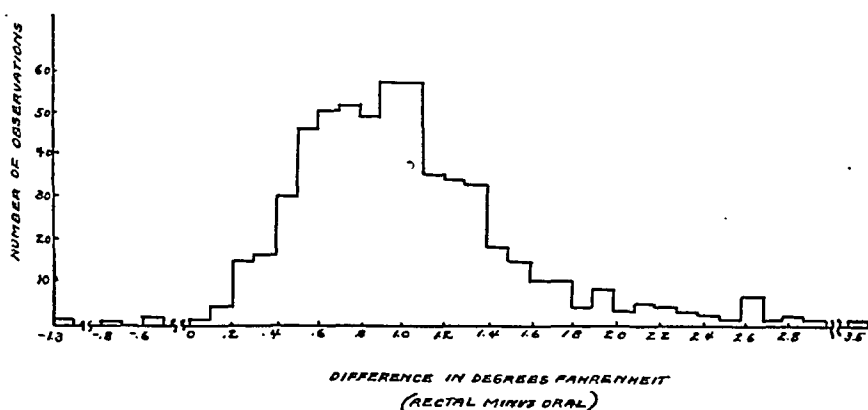


FIG. 1.—Variation of rectal minus oral differences in normal control subjects. Graph shows aggregate distribution of differences based on 24 simultaneous oral and rectal temperature measurements on 24 subjects.

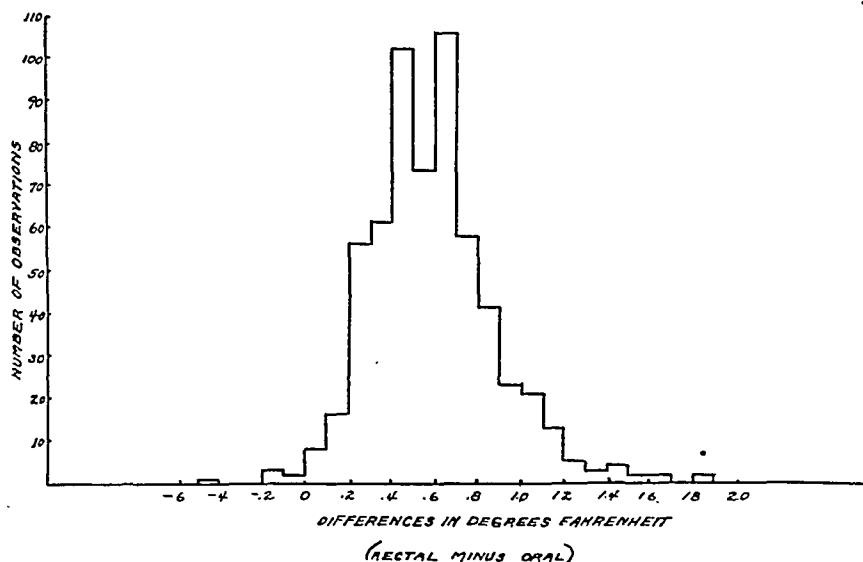


FIG. 2.—Variation of rectal minus oral differences in schizophrenic subjects. Graph shows aggregate distribution of differences based on 24 simultaneous oral and rectal temperature measurements on 25 subjects.

been pointed out in the description of methods and materials that the normal group was subjected to more varied conditions than the schizophrenic group. To what extent the smaller mean difference between oral and rectal temperatures in the patients was related

to the more constant conditions obtaining among them, and to what extent the difference may have represented a characteristic of the psychosis, these studies do not show. The problem is under further study.

Investigation of the correlations between the oral and rectal temperatures shows a striking difference between the normal subjects and the patients. In the normal group individual correlation coefficients range from $-.41$ to $+.91$, with an average of $+.56$. In some cases the rectal temperature tended to be low when the oral was high and *vice versa*, whereas in others the two varied together. In the schizophrenic group the range is from $+.20$ to $+.92$, with an average of $+.73$. This difference between the two groups may in part be evidence of the influence exerted by the greater variation of activity on the "normals." But even under the fairly constant conditions obtaining among the patients, the predictability of oral temperature from the rectal is of low degree. Among normal subjects the possibility of predictability becomes entirely illusory.

Detailed statistical analysis reported by us in another paper¹³ shows that in comparing the figures for "normals" with those for schizophrenics one finds that there is greater variability shown by the "normals." In the case of the schizophrenics no distinction can be made between the oral and rectal temperatures as to relative reliability. In the "normals" the rectal temperatures seem to show greater stability than the oral. These results suggest that in dealing with individuals such as the normal group, who are subjected to varying conditions of activity and of external temperature, the rectal measurement is a more reliable source of information. In individuals like our schizophrenic group, who are restricted in activity and not exposed to variations in external temperature, both rectal and oral measurements seem to be of equal reliability. Studies by Hoskins and Sleeper¹⁴ had suggested that abnormal variability of physiologic functions would be shown by the schizophrenics. This is not the case in the present study of body temperature.

Several authors state that hypothermia is a common finding in schizophrenia. Kraepelin¹⁵ says, "Temperature is usually low, sometimes sub-normal, with occasional reversal and small range of the daily fluctuations." Bleuler¹⁶ and Singer¹⁷ make similar statements. Langfeldt¹⁸ quotes several writers on this point, some of whom agree while others write of a rise of temperature for which no reason was found. Hypothermia was noted as a rather constant finding in the numerous studies of body temperature in mental and nervous diseases made in the latter half of the 19th century (Williams,¹⁹ Wunderlich,² Zenker,²⁰ Snell²¹). It seems impractical to take the results of studies made on body temperature in the psychoses before the general adoption of the Kraepelinian classification for comparison with the results of our present study, as the schizophrenic (dementia precox) group was not separated from the

other psychoses. There is in recent literature practically no reference to body temperature in schizophrenia.

In this study the normal subjects had a lower mean oral temperature than the schizophrenics and essentially the same mean rectal temperature (Table 1).

In this country and in Europe, 98.6° has been generally accepted as the "normal" body temperature of the healthy individual. Clinical thermometers have a mark at this level, and on clinical charts a heavy line is found at 98.6° . In British countries 98.4° has come to be regarded as the "normal." This figure is derived, as Pembrey² has pointed out, from the observations of John Davy, and represents the mean of observations of oral temperature taken on himself chiefly during the active part of the day, with very few observations between midnight and early morning. Investigators in thermometry (Pembrey,² Wunderlich,¹ etc.) have pointed out that these figures by no means cover the facts.

Some recent writers have pointed out that to accept the figures 98.6° or 98.4° as the normal body temperature is wrong. Lyon and Wallace²² found the mean axillary temperature in 250 non-febrile hospital patients confined to bed to be 97.2° at 7.00 A.M. and 97.45° at 7.00 P.M., with an average of 97.32° . They state that 98.4° is not the maximum reading above which the presence of fever may be assumed, and that it is inaccurate for patients confined to bed for long periods. Whiting²³ reports the mean oral temperature in 500 criminals as 98.37° and gives 98.38° as the mean for those prisoners apparently in perfect health. Paton²⁴ found in a study of the oral temperature in 108 healthy schoolgirls from 14 to 17 years of age that 75 per cent of the readings were below 98.4° . Rautmann²⁵ in a study of more than 1000 students from 18 to 22 years of age determined an average axillary temperature in males of 98.2° , with extremes of 96.4° and 100° ; in females a fraction of a degree lower.

Our results as shown in Table 1 support the contention that 98.6° or 98.4° should not be regarded as the normal body temperature. These latter figures were supposed to represent the mean temperature in a healthy individual and do not make allowance for the regular diurnal variations, the degree of activity, the external conditions, or take into account the probability that there is a range within which the temperature may vary in different individuals in health. In the "normals" the mean oral temperature ranged from an individual mean of 96.9° to one of 98.4° in the morning, and from 97.5° to 98.5° in the afternoon. These figures do not show the extreme minimum and maximum values for any one reading in an individual, which are 94.6° and 100.2° respectively. Study of the figures given for mean rectal temperatures in the "normals" reveals similar findings, as do also the figures given for the schizophrenics. It must be pointed out that patients met in clinical practice are

seen under more variable conditions than our "normals," and therefore under such conditions greater temperature fluctuations than reported here may be observed.

Summary. A study of the relation between oral and rectal temperatures measured simultaneously in 24 normal and 25 schizophrenic subjects is reported.

The mean oral temperature was 0.95° lower than the rectal temperature in the "normals" and 0.54° lower in the schizophrenic group.

A low degree of predictability of oral temperature from the rectal temperature in the non-active schizophrenic group is shown by the correlations obtained. In the active normal group predictability becomes impossible.

The normal subjects individually showed more variability than did the individual patients.

In the normal subjects rectal measurements were apparently more reliable as an indication of body temperature. Oral and rectal readings were apparently equally reliable for this purpose in the patients.

The normal subjects had a lower mean oral temperature than the patients and essentially the same mean rectal temperature.

The difference in the figures for the two groups may be in part accounted for by the greater activity of the "normals." The suggestion is made that the heat regulating mechanism in the schizophrenic subjects may be different than in the "normals."

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INSULIN THERAPY IN TUBERCULOSIS.

BY ANDREW L. BANYAI, M.D.,

CLINICAL DIRECTOR, MUIRDALE SANATORIUM, WAUWATOSA, WIS.; CLINICAL INSTRUCTOR
IN MEDICINE, SCHOOL OF MEDICINE, MARQUETTE UNIVERSITY, MILWAUKEE,
WIS.; PRECEPTOR IN TUBERCULOSIS, SCHOOL OF MEDICINE, UNIVERSITY OF WISCONSIN, MADISON, WIS.,

AND

GEORGE H. JURGENS, M.D.,

SENIOR RESIDENT PHYSICIAN, MUIRDALE SANATORIUM, WAUWATOSA, WIS.

(From Muirdale Sanatorium, Wauwatosa, Wis.)

THE problem of adequate nutrition is of utmost importance in pulmonary tuberculosis. A great many tuberculous patients are of normal weight, or their weight can be restored to normal by rest and exposure to fresh air, or in addition to these by local interventions, such as artificial pneumothorax, phrenic nerve block, etc. However, there is a definite group of patients who, in spite of appropriate therapeutic measures, stay undernourished. Mostly moderately and far-advanced cases belong to this class. In this group, attempts to correct the lack of appetite, to increase the food intake and to improve the nutritional status, often fail even when the well-known medicines, such as dilute hydrochloric acid and stomachics, are used; or when the diet is corrected and regulated, and constipation, if present, is eliminated.

We have used insulin for such patients having an active, moderately (24 cases) or far-advanced pulmonary tuberculosis (19 cases). This was based on the favorable results seen by Marriotte¹ and Barbour² in undernourished infants (1924), and by Falta³ in adults (1925) in a great variety of diseases, including tuberculosis. Investigations on the carbohydrate metabolism in the tuberculous were also highly suggestive in this regard. Rabuchin⁴ found in tuberculous animals a hypoglycemia during the first 2 weeks that became worse, returned to normal, or developed into hyperglycemia during the latter course of the disease. Necropsy revealed that there is a

tendency to a productive proliferative process in the pancreas, with atrophy and necrosis of the lobuli and contraction and sclerosis of the islands of Langerhans, resulting in hypofunction of the pancreas. Furthermore, the liver showed a very low glycogen content, the latter being the result of the increased metabolism caused by absorption of toxins or, as has been shown by Lawrence,⁵ by a shortage of insulin. Rabuchin⁴ also observed that following the administration of glucose orally or intravenously in tuberculous patients, there was a rapid, sharp and higher than normal rise in the blood sugar, followed by a slower return to its original level than seen in normal persons.

Several of the patients included in our group were strict bed patients. Only 8 were afebrile, 24 had temperature below 37.5 C (99.5 F). The temperature was between 37.5 and 38.5 C (101.3 F) in 8, and over 38.5 C in 3. Complications in these patients were: chronic interstitial nephritis, 1; renal tuberculosis, 1; renal and intestinal tuberculosis, 1; intestinal tuberculosis, 3; rectal fistula, 1; rectal fistula and Pott's disease, 1; tuberculous laryngitis, 4; tuberculous laryngitis and corneal ulcer, 1; pregnancy, 1; allergic asthma, 1; and ichthyosis, 1.

It may be thought that such patients might have represented, *a priori*, a poor prognosis and only slight opportunity, if any, to accomplish the desired effect. Still, such a selection seemed to be justified: 1, because tuberculous patients in the earlier or quiescent stages are, as a rule, in no need of forced nutrition; 2, because it was expected that, by inducing better ingestion, absorption and assimilation of food, one might be able to improve the condition of the body tissues and thus to increase the defense mechanism of the body in these stationary and often apparently intractable cases. It is a matter of conjecture that perhaps the effect of insulin on fat metabolism, as manifested by increased deposition of fats in experimental animals and in diabetics taking insulin, might favorably influence the course of tuberculosis. Animals kept on a high-fat diet showed better resistance against tuberculosis than those kept on ordinary diet; 3, because insulin may establish an increased endogenous production of insulin even after injections having been discontinued. Such an explanation was given by Metz⁶ for the maintenance of improved appetite and continued gain in weight after the termination of insulin treatment.

Our experience taught us that it is safer to begin the treatment with 5 units 3 times a day, $\frac{1}{2}$ hr. before meals, and increase it to 3 times 10 units or more daily, if necessary. This precaution is advisable because of the possibility of administering insulin to patients with hypoglycemia and thus causing a disagreeable reaction. Rabuchin⁴ found that the blood sugar was below 80 mg. per cent in 12.3% in pulmonary tuberculosis cases in Turban's first and second stage and in 22.4% in Turban's third stage. Six per cent of the cir-

rhctic, 25.5% of the productive nodular, and 28.8% of the exudative cases showed the same low blood sugar. The maximum amount of insulin given on one day was 3 times 15 units in this series. Only one patient went into a semicoma while taking 10 units 3 times a day. This patient had fever and a high pulse rate. Her appetite was not influenced by insulin and her food intake was not satisfactory. The reaction reached its peak in $3\frac{1}{2}$ hr. following the injection, during the afternoon "rest hours." It was promptly checked by intravenous glucose injection and by giving several glassfuls of orange juice with sugar. This occurrence probably could have been prevented by closer watch over the patient, and indicates the necessity of constant supervision of insulin treated patients. One patient developed abdominal pain, nausea and vomiting after each injection of 10 units of insulin, a condition not unlike that recently described by Williams⁷ as gastro-intestinal allergy due to insulin. In 1 case the insulin was discontinued because of headaches, dizziness and extreme weakness following injections, although the appetite showed marked improvement. Almost one-half of our patients reported slight weakness, tremor and shakiness prior to the development of hunger. It is a good policy to tell the patients about the probability of such mild hypoglycemic reaction, before the treatment is begun.

ALLERGIC SKIN REACTION. This was seen in 5 cases. Two of these developed generalized urticaria with intense itching; one on the 23d day, for 5 days; the other on the 10th day of her second course. Both of these patients were given 10 units 3 times a day. The 3d patient reported that a swelling the size of a large walnut, with slight tenderness, itching and redness, appeared at the site of each injection of 10 units. This reaction was first noticed during the second week of treatment and none was seen during the last 2 weeks of the 10 weeks' insulin treatment. His appetite showed great improvement after the treatment was stopped. In the 4th case of insulin hypersensitiveness, the appearance of a hard swelling with a superficial erythema at the site of injection began on the 8th day of the course during which 5 units were given 3 times a day. These reactions appeared in about 6 hr. and lasted for 2 days. No gain in weight was noted in this case, although the appetite became better and the amount of food ingested was greater than before. The 5th patient developed a slightly reddened, itching, hard swelling the size of a small walnut following injections of 10 units of insulin, which gradually disappeared in 2 days during the first 2 weeks of the course. This patient had excellent appetite in spite of these reactions. Both of these types of allergic reactions were analyzed by Tuft⁸ in detail. Allan and Scherer⁹ studied 100 cases in which allergic manifestations occurred during insulin treatment in diabetics. They found that reactions occur from insulin obtained from every source, although there were differences in the number of

reactions from different lots of insulin. We have not observed insulin hypersensitiveness in an about equal number of diabetics who also had pulmonary tuberculosis, prior to the use of insulin in non-diabetics. Nor have we seen allergic reactions in diabetics who were given insulin from the same lot used for our non-diabetic patients. It must be assumed that a possible profound change in the allergic status of patients with diabetes and tuberculosis is responsible for the absence of allergic reactions in the tuberculous diabetic.

Spontaneous desensitization occurred in 2 of our cases who had marked local reactions. In the urticarial cases the insulin was discontinued immediately. Allan and Scherer⁹ obtained relief from irritation by using insulin from a different source. Their efforts to bring about desensitization deliberately were not very satisfactory.

The diet of our patients consisted of the regular meals served to sanatorium patients, supplemented by milk, crackers and bread in the forenoon, afternoon and before retiring, according to their appetite.

Therapeutic Results. Of the 24 moderately advanced cases, 11 developed a marked, 7 a moderate and 1 a slight improvement of the appetite. No change was noted in 4, and the appetite became worse in 1. Of the 19 far-advanced cases the appetite greatly increased in 3, moderately in 4 and slightly in 4; it remained unchanged in 6, and became worse in 2. In those benefited by the treatment, the improvement was noticeable, usually, on the first day or during the next 2 to 3 days. The appetite remained good throughout the course of treatment in the great majority of cases. Lack of increase of appetite during, and appreciable increase after insulin treatment were seen in 2 patients who were treated for 2 and 10 weeks, respectively. The appetite became ravenous in some patients. The hunger appeared about $\frac{1}{2}$ hr. after the injection, with the exception of 1 patient whose insulin had to be given 15 min. before meals because of his early hunger reaction. Hunger during the forenoon, afternoon and 2 to 3 hr. after supper was reported by several patients. The appetite increased after the discontinuance of insulin in 5 moderately and 1 far-advanced case, remained improved but stationary in 11 and 9 cases in these respective groups, and diminished in 4 moderately and 8 far-advanced cases.

Gain in weight was recorded in 13 (54.1%) of the moderately advanced and in 9 (47.3%) of the far-advanced cases. This was maintained by the majority (69%) in the moderately advanced but only in 44% in the far-advanced group during the next 2 months of observation. Additional gain was recorded in 2 of the first group. Gain in weight was lacking during, but noted after the discontinuance of insulin in 2 patients of the first and in 1 of the second group. The gain in weight averaged 1 pound per week in several instances. The maximum average weekly increase was 2.9 pounds. The end-results showed as high as 11% gain in weight in 1 case, and between

5 and 10% in several patients. The largest individual gain was 13 pounds during the treatment.

The longest continuous treatment lasted for 17 weeks. One patient was given 2 courses which together lasted for 20 weeks. The length of treatment in the remaining cases was from 2 to 14 weeks. Attempted treatment or treatment which lasted less than 2 weeks was given in 1 case of gastro-intestinal insulin allergy, 1 case which developed semicoma, 1 with severe nervous reaction, and 3 with extreme weakness following injections. Of the 4 patients who had 2 courses, 1 developed a severe generalized allergic reaction, in 1 the response was not satisfactory, and improved appetite was noted in 2.

A transient elevation of the temperature which could have been attributed to insulin occurred in 2 instances. However, a close study of the temperature charts of these patients revealed a similar "auto-tuberculin" reaction prior to the use of insulin. Frank hemorrhage was not observed during the treatment. One patient who had it prior to the treatment had not developed any tendency to hemorrhage while on insulin. Streaked sputum was seen in 3 patients who had similar occurrence before. It cleared up by routine measures in a few days. We have not observed focal reaction in our patients which could have been due to insulin. On the contrary, improvement in the pulmonary process was found in 6 patients during or following the insulin treatment. Although we feel that this might have been a coincidence, it is reasonable to suppose that one might be able to aid resistance, defense, and repair by improving the nutritional condition of the tissues.

We found the following points of great practical importance: 1, The dosage should be adapted to the individual case; 2, severe reactions must be avoided by proper instruction of the patients as well as the nurses, with particular attention to the "rest hours" when the sanatorium patients, as a rule, are without direct supervision and when a coma may set in insidiously. Each patient must have an easily accessible supply of food of high carbohydrate content; 3, the tray of strictly bed patients must be checked after it is returned and, if it is found that insufficient amount of food was ingested, the patient should be given enough carbohydrates; 4, insulin must be discontinued in case of an urticarial reaction, while it may be continued in patients who react with an indurated swelling at the site of injection because these patients, usually, become desensitized spontaneously; 5, the injections should be discontinued if there is no favorable response in 2 weeks.

Summary. Observations on the effect of insulin in 43 non-diabetic patients with active, moderately and far advanced pulmonary tuberculosis are presented. Insulin therapy was found to be of value in that it improved the appetite in 19 (79.1%) of the 24

moderately advanced cases and in 11 (57.8%) of the 19 far-advanced cases. It increased the weight in 13 (54.1%) of the moderately advanced and in 9 (47.3%) of the far-advanced cases.

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THE CINCHOPHEN OXIDATION TEST OF LIVER FUNCTION IN PULMONARY TUBERCULOSIS.

BY JOHN B. O'CONNOR, B.A.,

HERBERT YOUNG, M.D.,

JOHN STEIDL, M.D.,

FIRST ASSISTANT RESIDENT PHYSICIAN,

AND

FRED H. HEISE, M.D.,

MEDICAL DIRECTOR, TRUDEAU SANATORIUM, TRUDEAU, N. Y.

LIVER damage varying in type and extent has been frequently noted at the autopsy table in patients dying of pulmonary tuberculosis. Two of us have shown¹ that if a variety of the currently accepted tests of liver function are used, this liver damage may be demonstrated during life in a high percentage of very ill patients with advanced disease. During the course of these studies we found the cinchophen oxidation test of hepatic function (Lichtman) to be the most sensitive; at least it gave the largest number of positive results among the liver function tests used by us.

Having demonstrated the frequency of liver damage in advanced disease, the question arose as to how frequently disturbance of liver function occurred in other types of our patients.

The incidence of liver function disturbance as demonstrated by the cinchophen oxidation test was determined in 115 consecutive, unselected patients admitted to the Trudeau Sanatorium. An attempt was also made to correlate liver function disturbance with the activity, extent and character of the pulmonary tuberculosis,

studying the symptoms of the patient, the Roentgen ray film, the leukocytic reaction according to Medlar's count and the blood sedimentation rate.

Briefly, the cinchophen oxidation test consists in feeding the patient 0.45 gm. of cinchophen and determining colorimetrically the output of oxycinchophen in the urine. According to Lichtman^{2*} 100 mg. or less of oxycinchophen are excreted in the urine of normal subjects. When an amount in excess of 100 mg. is found in the urine, liver insufficiency is considered to be present, higher figures indicating greater insufficiency. We have had almost no experience with this test other than with tuberculous patients, and therefore accept the status of the test as it appears in the literature.

Incidence. The incidence of hepatic insufficiency in this group of cases was very high. Among 24 cases classified minimal-A (American Sanatorium Association), 22 excreted more than 100 mg. of oxycinchophen, the average being 211 mg. Among 72 patients classified moderately advanced-A, 68 excreted more than 100 mg., the average being 194 mg. Ten patients classified far-advanced-A, all excreted more than 100 mg. Of 3 patients classified far-advanced-B, 2 excreted more, and 1 less than 100 mg. The far-advanced patients excreted an average of 207 mg. Thus 91% of minimal, 94% of moderately advanced and 92% of far-advanced cases showed evidence of hepatic insufficiency as determined by the cinchophen test.

Relation of the Cinchophen Oxidation Test to the Activity of the Disease. An attempt was made to correlate the degree of insufficiency, as indicated by the amount of oxycinchophen excreted, with other factors which have been found useful in the evaluation of activity of pulmonary tuberculosis.

Clinical Symptoms. Patients are regarded as symptomatically active or inactive largely on the basis of pulse and temperature, although when these are normal a patient is sometimes regarded as symptomatically active when he has marked fatigue or other symptoms. The symptomatically active patients in this series excreted an average of 210 mg. of oxycinchophen; those symptomatically inactive an average of 194 mg.

Roentgen Film. The activity of the disease was estimated on the basis of the first Roentgen ray film taken on admission. The patients whose films were interpreted as active excreted an average of 195 mg. Those whose films were interpreted as inactive excreted an average of 205 mg.

Patients whose disease was regarded as exudative on the basis of the Roentgen ray film excreted an average of 200 mg., while the excretion of the proliferative group averaged 194 mg. While the exudative group excreted a somewhat larger amount of oxycincho-

* We are indebted to Dr. Lichtman for aid, suggestions, and friendly criticism both by correspondence and on the occasions of his visits to our laboratory.

phen, there were striking individual examples of very low excretion with exudative disease, and very high excretion with proliferative disease.

Blood Sedimentation Rate. The sedimentation rate (Cutler method) was regarded as active when above 8 mm. in men and above 10 mm. in women. Patients with an active sedimentation rate excreted an average of 205 mg.; those with an inactive sedimentation rate an average of 193 mg.

Leukocyte Count. Patients with a normal count excreted an average of 193 mg., those with a resistant count 197 mg., and those with a hyperplastic count 115 mg. As only 3 patients fell into the last group, this figure has little significance. Patients with a septic count excreted an average of 202 mg. of oxycinchophen.

It is apparent that there is little variation in the amount of oxycinchophen excreted by individuals in the active and inactive groups, judged by any of these criteria. Furthermore, a few cases were also noted in which there was marked activity of the disease and a normal excretion of oxycinchophen and *vice versa*.

Comment. If the cinchophen oxidation test is to be relied on, it is apparent that hepatic insufficiency occurs in a very high percentage of all types of pulmonary tuberculosis. In an effort to determine the duration of this insufficiency and its relationship to the clinical course of the diseases, the test is now being repeated periodically on a group of patients.

An attempt to correlate the activity of the pulmonary tuberculosis with the excretion of oxycinchophen has been disappointing and it is apparent that this test is not equal in practical clinical value to other accepted criteria of activity. The results suggest that, even though the foci of pulmonary tuberculosis may become clinically quiescent, secondary functional or organic hepatic changes may persist indefinitely in many patients. We hope to acquire more definite information on this point during studies which are now in progress.

There may be unknown factors involved in tuberculosis that cause the abnormal oxidation. Apparently mechanical factors, such as the volume of diseased lung or the presence of pneumothorax, have no important influence on the oxidation of cinchophen.

Conclusions. Hepatic insufficiency, as indicated by the cinchophen oxidation test of hepatic cell function, occurred in more than 90% of a group of consecutive unselected patients with pulmonary tuberculosis admitted to Trudeau Sanatorium.

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GAUCHER'S DISEASE.

REPORT OF A CASE WITH PRESENTATION OF A TABLE DIFFERENTIATING THE LIPOID DISTURBANCES.

BY AARON CAPPER, M.D.,

ASSOCIATE PEDIATRIST,

HERMAN EPSTEIN, M.D.,

ASSISTANT PEDIATRIST,

AND

ROBERT A. SCHLESS, M.D.,

CHIEF PEDIATRIST, JEWISH HOSPITAL, PHILADELPHIA, PA.

(From the Pediatric Service of Dr. Robert A. Schless, Jewish Hospital.)

SEVERAL reasons prompt us to report the following case of Gaucher's disease. 1, The number of authentic cases reported is still sufficiently small to warrant placing an additional one on record; 2, an error in the diagnosis made during the earlier admission of this girl makes it important to stress that point in order to prevent its repetition; 3, this patient's condition since she was subjected to splenectomy is instructive; 4, microincineration of sections of the spleen has not been done heretofore in this disease; 5, the results of the chemical examination of the spleen for kersin are worth noting.

Gaucher's disease is generally understood not to be hereditary in character, and thus far Anderson's¹ is the only hereditary case that has been reported. It is now regarded as a congenital, primary and familial constitutional disease in which the lipoid kersin, belonging to the cerebrosids, is stored in foam cells, measuring usually 20 to 40, and occasionally up to 100 microns in diameter, the so-called Gaucher cells; these, according to Pick,³ are derivatives of the reticulum cells (especially so in the spleen) and they invade the spleen, liver, lymph nodes, and bone marrow and, if the disease occurs in infancy, also the thymus, tonsils, lymph tissue of intestines, lungs, and even the cerebral cortex. The substance kersin, the chemical formula of which was given by Rosenheim⁴ as $C_{47}H_{91}NO_8 \cdot H_2O$, is a compound having properties very similar to phrenosin, and accompanies phrenosin in tissues of the nervous system, both constituting a cerebrosid or glycolipin. On acid hydrolysis, kersin yields lingoceric acid ($C_{24}H_{48}O_2$), sphingosin and *d*-galactose.

Gaucher's disease shows a particular predilection for individuals of the Jewish race. It is more common in females, occurring in the proportion of about 2 to 1. It is characterized by a slow and insidious onset, a gradual enlargement of the spleen, followed later by an increase in the size of the liver. The patient develops a hypochromic anemia, thrombopenia, and a leukopenia, due to infiltration of the bone marrow by foam cells. Hemolysis is an additional



FIG. 1.—Note the Erlenmeyer-flask appearance of lower ends of both femora. Irregularity of cortex probably due to previous operations. Areas of osteolysis are also characteristic of Gaucher's disease.

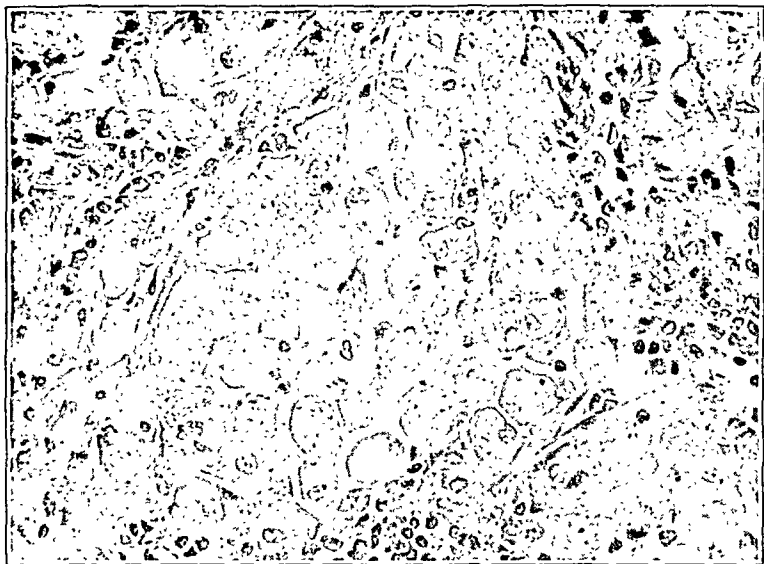


FIG. 2.—High power: Section of spleen shows nests of large Gaucher cells possessing eccentric nuclei and considerable clear protoplasm. Most of the cells possess one nucleus; a few are multinucleated. Cells are fairly uniform in size. They are surrounded by connective tissue.

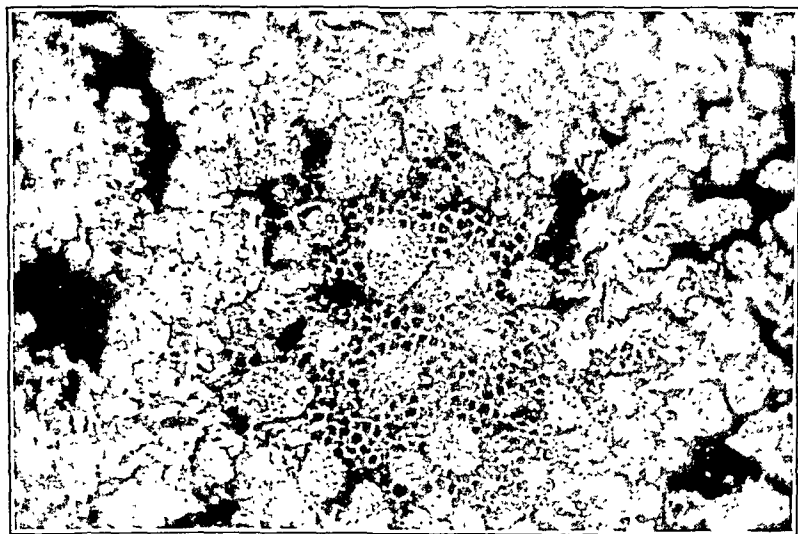


FIG. 3.—Section of splenic tissue after microincineration. Note the normal amount of inorganic material in the cytoplasm of the Gaucher cells and the high concentration of ash in the peripheral zone of the nuclei.

factor in the production of anemia. Enzer,² in the discussion of Anderson's case, says that leukopenia is not necessarily characteristic and essential for the diagnosis; he saw 3 cases of Gaucher's disease which showed a rather marked leukocytosis. About $\frac{1}{2}$ of the patients develop pigmentation of the exposed skin, which depends upon the hemosiderin liberated as a result of increased blood destruction. A prominent and supposedly characteristic finding mentioned by many authors is the yellow-wedge-shaped pinguecula of the sclera or conjunctiva. It appears now that this sign is not present as frequently as had been thought, occurring in only 14 out of 89 cases summarized by Hoffman and Makler.⁵ It is even less common in children; present in only 10% of cases. The large spleen may be found only accidentally in the course of a general examination, as in our case. The patient may complain of a variety of symptoms related to the osseous system. Some may only have vague pains in the limbs or joints, giving rise to the diagnosis of "growing pains," or, as in the case of Milch and Pomeranz,⁶ to "rheumatism." In others the pain may be acute and violent, and lead to the mistaken diagnosis of acute osteomyelitis, as was true in our case, in an additional one reported by Milch and Pomeranz,⁶ and in 1 of the 2 cases reported by Potter and McCrae.⁷ This tenderness or pain in the bones is probably due to the increased subcortical pressure caused by the infiltrating masses of Gaucher cells. In some patients the only complaint is that of pain or tenderness in the region of the spleen, or the patient's attention is drawn to the enlarged abdomen. When the blood platelets fall to a sufficiently low number there frequently ensue blood extravasations into the skin or mucous membranes, although there is no direct proportion between the number of platelets and the bleeding phenomena. In our patient, purpuric spots did not appear on the face, forearms, and conjunctivæ until the platelets dropped to 40,000; and yet, on a later occasion, when they were 29,400, she had no hemorrhages.

Gaucher's disease does not produce cerebral symptoms except in infancy, when various neurologic findings may predominate, thus simulating Niemann-Pick's disease. Oberling and Woringer⁸ refer to the syndrome of opisthotonos, spasticity, strabismus, and nuchal rigidity in infancy as "progressive decortication." Moncrieff⁹ reported this syndrome in a 10-week-old infant. These cerebral manifestations are probably due to the infiltration of foam cells in the cerebral cortex and other parts of the brain.

We offer the following table of the known diseases of lipid metabolism, to delineate the similarities and contrasts of these disturbances related to Gaucher's disease.

Case History.—M. K., Jewish girl, aged 10 years, was first admitted on May 1, 1929, at the age of 6½ years. Her past medical history is negative. Her father, mother, 3 brothers and 1 sister were examined for Gaucher's disease and found to be negative. The chief complaint on admission, was pain and swelling of the right thigh just above the knee of several days'

TABLE 1.—XANTHOMATOSSES OR LIPOIDOSES—DISEASES DUE TO DISTURBANCES IN LIPOID METABOLISM.
(Pick.)

Name.	Type of lipid	Blood findings.	Eye grounds.	Spleen, liver glands.	Age.	Bones.	Pathognomonic features.	Skin.	Treatment.	Remarks.
A. Gaucher's disease (90-100 cases)	Cerebrosid (kerasin-A sphingogalactid)	1. Hypochromic anemia 2. Leukopenia 3. Thrombopenia 4. Later, hemorrhagic diathesis	Negative	Spleen markedly enlarged Liver enlarged Slight or no lymph-adenopathy	Infancy to adult life	Mottling and rarefaction with cortical thinning, flasklike appearance ends of femora	1. X-ray appearance of long bones, especially femora 2. Splenic puncture 3. Bone-marrow examination	Subicteric pigmentation of exposed parts in 45%. Yellow thickened pinnae in 15%	Splenectomy (fatal in 20%) or radiation (both palliative)	Common in Jews.
B. Niemann-Pick's disease or lipid histiocytosis (Bloom)	Phosphatids	1. Moderate secondary anemia 2. Slight leukocytosis 3. Vacuolization of non-granulated cells 4. Excess of lipoids in blood	Cherry-red spot in macula lutea <i>occasionally</i> found	Spleen and liver very large Moderately lymph-adenopathy	Infancy	Any bones or organs may be invaded by the foam cells	Splenic puncture	Brownish-yellow discoloration	No treatment, all fatal	Mental retardation may be present resembling Tay-Sachs' disease. Most common in Jews.
C. Hand-Schüller-Christian disease (45-50 cases)	Cholesterol and its esters	There may be a hypercholesteremia	Negative	Not enlarged	Any age	Membranous bones involved	1. Defects in membranous bones 2. Diabetes insipidus 3. Exophthalmos 4. Gingivitis and stomatitis 5. Adipose genital dystrophy	Negative	X-ray treatment of involved area causes prompt local healing but does not stop the progress of the disease.	
D. Tay-Sachs' disease or amaurotic familial idiocy	A prelipoid	Negative	Cherry-red spot in macula lutea <i>usually</i> found	Usually negative	Infancy	Not involved	1. Eye grounds 2. Mental retardation 3. Hyperacusis	Negative	All fatal	Brain shows prelipoid deposits in granular layer and about dendrites of the Purkinje cells. Most common in Jews.
E. Xanthomatosis of skin, etc.	Cholesterol and its esters	Negative	Negative	Negative	Any age	Any bones may be involved	Xanthomatosis of any part of skin	Excision, if tumorous.	

duration. Her temperature was normal and rose to 100.8° 2 days following operation, when it again dropped to normal and remained so until her discharge. The right femur was trephined, free "pus" obtained, a drain inserted and Dakin solution dressings applied. The wound healed in 3 weeks. *It should be noted at this time that the smears and culture of the "pus" obtained were negative.* Her next admission was over a year later, on May 17, 1930, because of pain in the center of the left thigh, which began 24 hr. previously. The temperature was 100.2° . The Roentgen ray of the left femur showed a slight irregularity of its shaft, just below the middle third, with some decalcification just above the knee joint. A diagnosis of acute osteomyelitis of the left thigh was made and the femur was trephined and drained. *The exudate at operation was gummatous in character, and a smear and culture were negative.* Eight days after operation, when her wound was still draining and her temperature was elevated to 100.2° , her white cell count was 6000, the first report of a leukopenia. She was discharged as cured on June 6, 1930.

Her 3d admission took place on July 8, 1930, 1 month later, because of redness, swelling, and tenderness of the left femur over the scar of the previous operation. *Her temperature was 100° F., and the white cell count was only 6000, again a leukopenia.* The medullary cavity of the left thigh was curetted, and a sequestrum removed. She was given a blood transfusion of 125 cc. On August 12, 1930, it was discovered by one of us that the spleen was very much enlarged, reaching down to the pelvic brim. The liver was increased in size, though not as much as the spleen. Although this was the first time that the enlarged spleen and liver were noted, it is probable that they had been so for some time, but were overlooked on account of the concentrated attention on the lower extremities. The nurses remarked that the patient's abdomen had been unduly prominent for some time. The mother later stated that the patient always had a definitely prominent abdomen. At this time on account of the history of osteomyelitis, a peculiar waxy pale complexion, a hemoglobin of 31%, continuous albuminuria and a complicating diarrhea together with the splenomegaly, a provisional diagnosis of amyloidosis was made. On August 14, 1930, the roentgenologic examination showed small areas of decalcification with a *slight widening of the diaphysis near the knee-joint*, which were interpreted as being the result of a chronic osteomyelitis. The right humerus, lumbar vertebrae and sacroiliacs appeared normal. Her 4th admission on August 13, 1931, was for the purpose of draining a superficial abscess of the left thigh.

Her fifth admission on October 3, 1931, was for the purpose of determining the cause of the splenomegaly and anemia. Her general physical condition was unchanged. She was pale and there was no definite pigmentation except that her face showed elements of pigment, reminding one of the facies of a pregnant woman, the so-called "chloasma uterinum." The conjunctivæ showed no pigmentation. The Mantoux test was negative. The two significant findings at this time were the leukopenia, 6500 white cells on October 5, 1931, and the thrombopenia, 50,000 platelets on October 6, and 55,000 3 days later. This was the first time that a thrombopenia was found; Gaucher's disease was suspected and a splenic puncture advised. The parents refused permission for the procedure and the patient was discharged 17 days after admission. Her 6th admission on May 27, 1932, was for the purpose of curetting a sinus in the left leg.

The 7th time she came in on January 7, 1933, because the spleen was slowly increasing in size. The upper border of the liver was found by percussion in the 4th interspace, while the lower border was $1\frac{1}{2}$ inches below the costal margin. The upper border of the spleen was at the 5th rib in the axillary line, the lower border was 2 inches below the crest of the ilium, and the right border reached to the midline. It was not tender on palpation.

TABLE 2.—BLOOD STUDIES IN A CASE OF GAUCHIER'S DISEASE (4½ YEARS).

Date.	Hemo- globin, per cent.	Red cells in millions.	White cells in thous- ands.	Neutro- phils, per cent.	Lympho- cytes per cent.	Large mononu- clears, per cent.	Transi- tionals, per cent.	Eosino- phils, per cent.	Platelets in thous- ands.	Reticulo- cytes, per cent.	Special.
May 1, 1929	71	4.0	15.5	69	31						
May 17, 1930	64	4.0	9.2	65	35						
May 25, 1930		4.65	6.0	52	47	1	1	Slight anisocytosis.
July 9, 1930	60	2.1	7.4	57	41	1	1	Some aniso- and poikilocytosis.
July 25, 1930	31	2.0	7.1	58	42	Marked anisocytosis and achromasia.
July 26, 1930	30	2.55	5.4	75	25	1 Türk cell; 2 days after transfusion.
July 31, 1930	40	2.6	13.3	56	44	Many poikilocytes.
Aug. 2, 1930	42	2.5	7.1	50	49	..	1	
Aug. 12, 1930	44	2.6	6.6	59	41	
Aug. 13, 1930	42	3.3	6.6	59	41	330	0.1	Marked anisocytosis.
Aug. 14, 1930	50	3.0	5.2	50	50	2	3	Marked anisocytosis.
Aug. 15, 1930	50	3.0	5.2	48	47	Some anisocytosis.
Aug. 16, 1930	53	3.0	4.8	42	48	..	1	Slight anisocytosis.
Aug. 27, 1930	67	4.05	5.3	59	40	..	2	
Sept. 5, 1930	67	3.9	7.0	54	44	
Sept. 22, 1930	70	4.45	7.2	65	35	50	0.4	B.T. 5 min., C.T. 5½ min.
Sept. 28, 1930	57	3.85	6.8	60	40	..	2	..	55	...	Hemol. begins at 0.44, hemol. complete at 0.32.
Oct. 5, 1931	56	3.35	6.5	43	55	65	1.0	1 Türk cell. C.T. 4½ min. Clot retraction delayed.
Oct. 9, 1931	45	...	B.T. 5 min., C.T. 2½ min.
Jan. 10, 1933	81	4.6	7.0	52	44	2	65	...	Hemol. begins at 0.44, hemol. complete at 0.32.
Jan. 23, 1933	80	4.8	5.0	40	60	40	...	Day of operation.
Jan. 27, 1933	45	...	
Jan. 30, 1933	65	...	
Feb. 7, 1933	77	4.3	5.0	44	56	30	...	
Feb. 11, 1933	76	4.2	5.0	44	56	29	...	

AFTER SPLENECTOMY AND TRANSFUSION OF 225 CC. OF BLOOD.											
Date.	Hemo- globin, per cent.	Red cells in millions.	White cells in thous- ands.	Neutro- phils, per cent.	Lympho- cytes per cent.	Large mononu- clears, per cent.	Transi- tionals, per cent.	Eosino- phils, per cent.	Platelets in thous- ands.	Reticulo- cytes, per cent.	Special.
Feb. 12, 1933	85	4.9	16.0	82	12	5	1	..	177	...	C.T. 2½ min.
Feb. 13, 1933	87	5.0	14.1	73	18	7	..	2	1,238	...	
Feb. 15, 1933	900	...	
Feb. 16, 1933	530	...	
Feb. 18, 1933	500	...	
Feb. 21, 1933	90	4.95	10.5	63	29	5	..	3	550	...	
Feb. 23, 1933	80	4.7	12.0	74	23	..	2	1 baso- phil	495	...	
Feb. 28, 1933	1 baso- phil	277	...	
July 25, 1933	83	4.6	14.6	72	27	200	...	B.T. 3½ min. C.T. 3½ min.
July 28, 1933	75	4.2	8.2	50	49	1	405	...	
Oct. 12, 1933	76	4.05	9.8	53	47	

B.T. = Bleeding time.

C.T. = Coagulation time.

A uroselectan test showed a first degree hydronephrosis of the left kidney, which was confirmed by the urologist on cystoscopic examination, and was thought to be due to mechanical pressure by the large spleen. On January 24, for the first time, numerous purpuric spots appeared on the face, fore-arms and conjunctivæ. The tourniquet test was positive. The platelet count fell to 40,000. The next day, purpuric spots appeared on the lower extremities. These gradually cleared even though the platelets subsequently fell to 29,400. The eye grounds were normal. The roentgenologic examination of February 1, by Drs. Leon Solis-Cohen and Samuel Bruck revealed in the femora "a typical Erlenmeyer-flask-like appearance, due to widening of the shafts at their distal portions and a narrowing at the junction of their middle and lower thirds; findings characteristic of Gaucher's disease. The normal flaring observed at the femoral condyles was absent. In support of Gaucher's disease there was also a slight sclerosis of the head of the tibia and the presence of transverse growth lines in the fibula. The other long bones and the vertebral column showed no abnormalities."

She was subjected to splenectomy (Dr. Moses Behrend) on February 11 for several reasons. (1) The large spleen was becoming burdensome. (2) The pressure exerted on the left ureter was apparently causing hydronephrosis. (3) It was felt that the bleeding phenomena and the low platelet count could best be controlled by removal of the spleen. (4) Due to the downhill course of the patient it was decided to operate while she was still in good condition. The large spleen was found to be free from adhesions and was removed without difficulty. A blood transfusion of 225 cc. was given immediately following operation. A fresh smear of splenic tissue was examined by Dr. Edward Steinfield; it was found to contain typical foam cells which were very numerous, occupying most of the tissue. Within 24 hr. after splenectomy, the platelets rose to 177,000 and in another 24 hr. to 1,238,000. On February 28, 3 days before the patient was discharged, the platelets were 277,300 and the white count was 12,000. She made an uneventful recovery and was discharged in good condition.

TABLE 3.—OTHER LABORATORY STUDIES.

Date.	Blood Wassermann.	Blood cholesterol.	Blood chemistry.	Special.
Aug. 14, 1930	Negative			
Aug. 16, 1930	166 mg.	Non-protein nitrogen 25 Serum albumin 3.5 Serum globulin 2.6 Total protein 6.25	Urine—Faint trace albumin, sp. gr. 1010-1036, 1-6 W. B. C. per low-power field.
Oct. 6, 1931	134 mg.	Blood sugar 91 Urea 17 Non-protein nitrogen 26 Serum albumin 5.6 Serum globulin 2.0 Total protein 7.6	Icterus index, 5.0. Direct Van den Bergh neg. Indirect Van den Bergh 0.1. Stool negative for occult blood, ova and parasites.
Jan. 30, 1933	P. S. P. First specimen 30% Second specimen 35%	147 mg.	Galactose test: First — 85 cc.) Second—205 cc.) Third — 20 cc.) 1.7 gm. Fourth—185 cc.) Fifth —215 cc.)
Feb. 9, 1933	Icterus index 13.8.
July 25, 1933	Type IV blood	142 mg.	Blood sugar 84 Urea 9	Urine—Trace of albumin to none, sp. gr. 1003-1036. Double refractive bodies absent. 1-10 W. B. C. per low-power field.

The chemical examination of the spleen revealed 6.02% content of kersasin.

On July 23, 1933, she was admitted for the 8th time on account of a superficial abscess of the soft tissues of the left thigh, which was incised and drained. No involvement of the periosteum or the shaft of the bone was noted. The child had grown considerably and improved markedly in health since the splenectomy. She had gained 15 pounds in weight.

PATHOLOGIC REPORT (Dr. Samuel Levine). *Gross Description.* "The spleen weighs 1400 gm. The capsule is thickened, having a morocco-leather appearance. The splenic notches are well preserved. On section, the spleen appears very dense in consistency and fleshy in texture. It is deep red in color. Numerous light-grayish specks are noted; the follicles are not easily made out and the splenic pulp presents throughout a fine reticulum of grayish strands. The vessels were injected with formalin to preserve the vascular architecture."

Histology. "A section of the spleen shows destruction of the greater part of the lymph follicles. The sinusoids are occupied by a large number of Gaucher cells having an alveolar arrangement. The cells lie in close proximity to the red blood cells of the splenic pulp. The cells vary in size and shape. Some are oval, others are compressed and elongated, and still others are circular and polygonal in shape. The majority of the cells have a single nucleus, which is fairly well defined and eccentrically located. The cytoplasm is acidophilic and homogeneous in character. A few of the cells are multi-nucleated. Some of the Gaucher cells contain vacuoles. The staining property of these vacuoles serves to differentiate them from histiocytes. Some of the nuclei contain striations running a parallel course. On transverse section to the longitudinal diameter of the cells, these striations appear as stipples. The spleen is loaded with Gaucher cells which occupy a major portion of the organ."

Microincineration studies of the spleen were carried out for us by Dr. Esmond R. Long¹⁰, in order to determine whether a corresponding accumulation of inorganic material accompanies that of the cerebrosid kersin. "In general, the Gaucher cells were found to have a high content of ash in the nucleus and a low content in the cytoplasm as illustrated in the accompanying figure. Most investigators who have reported on incineration of tissues have called attention to the nuclear ash. In the study here reported the same peripheral distribution of ash was noted as described by Scott and Horning¹¹ in the nuclei of tumor cells and by Cowdry¹² in the nuclei of liver cells in yellow fever. The nucleoli conspicuous in the sections stained with hematoxylin and eosin could also be observed in the ashed specimens, although not with regularity.

"There was nothing distinctive in the distribution of the ash in the cytoplasm. Iron salts, which can be recognized by their color in ashed sections, were not observed. Degenerated cells, poor in material with staining affinity, were also poor in ash, and the large vacuoles characteristic of these cells in the usual preparations were seen in the corresponding incinerated cells. The appearance of the erythrocytes (accompanying figure) was characteristic. The ash was concentrated at the peripheral border. Presumably this was an artefact caused by the fixation and drying of the specimen. However, the peripheral distribution of ash was as marked as that in the nuclei, and if one is an artefact of fixation, the question is properly raised whether the other is not also. The total ash of a specimen from this case, incinerated in a crucible, was 27% of the dry weight. This may be compared with the figure of 15% of the moist weight, or approximately 6% of the dry weight, commonly given for the normal spleen.¹³ The incineration study furnishes the explanation for this decrease in ash per unit of weight. The ash is concentrated in the nuclei, and nuclei are present in much larger numbers per unit of volume or of weight in the normal spleen than in the spleen in

Gaucher's disease, the bulk of which is largely due to the cytoplasm of Gaucher's cells or cerebrosid cells, which is relatively poor in mineral matter."

Chemical Examination. The spleen was examined by Dr. John G. Reinhold and found to contain 6.02% of the dried spleen; this is now considered to be quite distinctive of Gaucher's disease. The figure of 6.02% really represents a minimal amount, for it was obtained after the recrystallizing of the chemical material 2 times. Kerasin may make up as much as 10% of the dried spleen, and in one of Cushing and Stout's¹⁴ cases, the crude cerebrosid made up almost 16% of the alcohol extract. The average amount of kerasin in Gaucher's disease reported by most investigators falls within the percentage content found in our case. Phrenosin was also found to be present.

Comment. There are a number of features in this case that deserve special emphasis and discussion. In the first place the question naturally arises, did this child have osteomyelitis and then develop Gaucher's disease, or were her bone affections due to Gaucher's disease primarily? It will be noted that, except for the white cell counts on May 1 and 17, 1929 (15,500 and 9220), she exhibited a leukopenia on practically all other occasions, in spite of the fact that she was supposedly suffering from an acute infectious and pyogenic process. At no time did she really show a septic or even high temperature. On several occasions she had a normal temperature in the presence of pain and swelling of the thighs; and on none of her admissions on account of "acute osteomyelitis" was she toxic. It will be recalled that at the first two operations on the right and left femora the smears and cultures were negative, a finding not expected in acute osteomyelitis. Furthermore, the surgeon noted that the exudate on her 2d admission was *gummatous* rather than purulent, suggestive of Gaucher material. On her 3d admission (August 14, 1930), the roentgenologist already noted a "slight widening of the diaphysis near the knee-joint," apparently the beginning or first stage of the characteristic "Erlenmeyer-flask-like formation." For the above reasons we believe that this patient did not originally suffer from acute osteomyelitis, but that her symptoms were due to Gaucher's disease. Due to operative intervention, pyogenic organisms were introduced from without, leading to secondary bone infection with its subsequent sequestrum formation. It is interesting to remark that in our case the leukopenia preceded the thrombopenia by 16 months. Also, almost 1½ years elapsed between the first finding of a low platelet count and the appearance of hemorrhagic phenomena. It is also worth noting that hemorrhages did not occur until the platelets fell to 40,000.

Realizing that splenectomy in Gaucher's disease is attended by a 20% mortality, we naturally hesitated to advise operation. Our reluctance was further enhanced by Pick's² observation that the bones may become more intensely affected following splenectomy. However, in view of the sudden change in the child's condition, the

slight increase in the size of the spleen, the hemorrhagic phenomena, and the continued decrease in platelets, operative interference was deemed a measure of necessity. The splenectomy brought about a normal blood picture and relieved the child of a burdensome abdominal mass which was beginning to cause harmful pressure on the left ureter. The removal of the spleen also improved the child's general health, as she has gained 15 pounds in the 5½ months subsequent to operation. In order to observe whether any changes had occurred in the long bones since the removal of the spleen, we subjected the patient to another roentgenologic study on October 8, 1933. Dr. Leon Solis-Cohen reported no change in the osseous system since the last films were taken, 8 months previously.

We see therefore, that thus far the splenectomy caused no deleterious effect in the osseous system and that it produced a general physical as well as hematologic improvement in her condition. It is, of course, to be remembered that this is a general metabolic disease in which many organs are involved. It is hardly to be expected that the removal of the spleen should effect a cure. The best that can be hoped is a symptomatic improvement and, by removing a large store of Gaucher cells, perhaps temporarily to arrest the course of the disease.

Summary. 1. A case of Gaucher's disease in a Jewish girl is reported that was originally diagnosed as acute osteomyelitis because of the predominance of bone symptoms.

2. Blood counts over a period of 4.5 years showed that leukopenia preceded thrombopenia by about 16 months, and hemorrhagic phenomena did not occur until the platelet count fell to 40,000.

3. Splenectomy produced a cessation of bleeding and persistently normal platelet and white cell counts. The patient gained in weight and improved generally. Thus far, 8 months since splenectomy, there is no clinical or roentgenologic evidence of progression of the disease.

4. The chemical examination of the spleen showed 6.02% of kersasin.

5. Microincineration studies showed a decrease in ash per unit of weight, the Gaucher cell cytoplasm being relatively poor in mineral matter.

6. A chart is appended illustrating the similarities and contrasts of Gaucher's disease with the other diseases due to disturbances in lipid metabolism.

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ARTHRITIS, ANABOLIC NUTRITION AND HEALTH.

A STUDY OF THE NOURISHMENT AND HEALTH OF JOINTS.

BY FRANCIS LOWELL BURNETT, M.D.,

AND

FRANK ROBERTS OBER, M.D.,

BOSTON, MASS.

(From the Health Class for Arthritis at the Peter Bent Brigham Hospital.)

Arthritis, the Anabolic Processes and Cell Regeneration. A failure of nutrient substances to construct or preserve normal bone and cartilage, *i. e.*, a metabolic disorder, has been often considered as the cause of arthritis. Perhaps the atrophy of bone in one type and the loss of cartilage and growth of osteoid tissue in the other type of the disease found by Nichols and Richardson¹ are chiefly responsible for this point of view; because in their basic study "faulty metabolism" is favored as the etiologic agent. This kind of malnutrition from gastro-intestinal disturbances may cause the lesions; for instance, Minot² writes that "little is known concerning the difficulties of absorption and utilization of food products from the digestive tract and regarding what particular food factors may improve gastro-intestinal function. . . . It is probable that significant degrees of such disturbances may arise in arthritis and be overcome by well-chosen diets." Some of these disturbances may be corrected by the diet of Fletcher and Graham;³ for, with the consequent improvement in haustral action, the improved colonic functions appear to favor the nourishment of the joints. In other treatments for this disease, however, as the doctor generally gives dietary directions or patients themselves correct erroneous ways of eating, health is sometimes restored. The result may easily then be ascribed to a natural remission, the administration of drugs, the use of baths, the manipulations of posture, or the injections of proteins or vaccines, if the beneficial effects of right eating and improved absorption on health are not recognized.

Variations in the consumption of food evidently influence its absorption. For by the correction of certain erroneous ways of

eating and living with better functioning of "the secondary digestive pouch"—the proximal colon—the intestinal contents are finally molded into uniform and firm segments, and thus the absorption is improved.⁴ (Fig. 1.) The results of this action, by the formation of the entirely segmented or normal feces, are shown in Fig. 2. Such a molding of the colonic contents produces not only these feces but also the normal intestinal rate.* Together these indices signify the complete digestion and absorption of food. Then, if nutrition is defined as the sum of the processes by which an animal absorbs food, and assimilation is the most important phase of the process,⁵ the operation of the proximal colon evidently creates a better kind of tissue construction. Since this process suggests improved assimilation, it has been called "anabolic nutrition."⁶ In the application of this kind of nutrition to the treatment of disease, a morbid process causing a deficiency or metabolic disorder appears to be replaced by a vital process restoring a state of health. The effect of this change on a superficial tissue may be seen by a comparison of the psoriatic lesions shown in Fig. 3 with the healthy skin of the same person shown in Fig. 4. Such a regeneration of cells following the establishment of anabolic nutrition has relieved this disease in a sufficient number of patients to indicate that spontaneous remissions are not being dealt with.^{7,8} As psoriasis is sometimes associated with and is often followed by arthritis, it is suggested that both diseases may be due to malnutrition from the passage of nutrient substances through the digestive tract instead of into the body. The results of malabsorption in deficiency diseases has been pointed out by Burnett and Howe.⁹ Of interest also, in the treatment of arthritis as a deficiency disease, is the regeneration of bone cells to relieve experimental scurvy described by Wolbach and Howe.¹⁰ They write that during the disease "the osteoblasts . . . assumed the shapes of fibroblasts" . . . but "the administration of orange juice . . . was followed promptly by the deposition of bone matrix between the fibroblast-like cells." Finally, the arthritic-like lesions produced in guinea pigs from a scorbutic diet alone, and from this diet and an infection, by Rinehart, Connor, and Mettier,¹¹ still further confirm the metabolic theory of arthritis.

The Creation of Anabolic Nutrition and the Treatment of the Joints.
To remove the cause of the arthritis through anabolic nutrition,

* The intestinal rate is an index of absorption, by which the contribution of one meal to the construction of the body is determined. To make the test, from 25 to 50 cc. of French millet seeds or 100 gr. of charcoal are swallowed immediately after an evening meal, and then the number of hours that elapse from the time the marker was ingested to the time the seeds or charcoal are first and last seen in the dejections is observed. In adults producing segmented feces, 1 and 2 dejections are common daily, yet the marked meal takes about 62 hrs. to appear in, and 134 hrs. to disappear from the feces. This rate is considered normal. (Burnett, F. L.: *Am. J. Roentgenol.*, 10, 359, 1923.)



FIG. 1.—A roentgenogram of the large intestine after a barium meal, showing outlines of the "digestive pouch" formed by the proximal colon and of the uniform masses of the segmented feces in the distal colon.

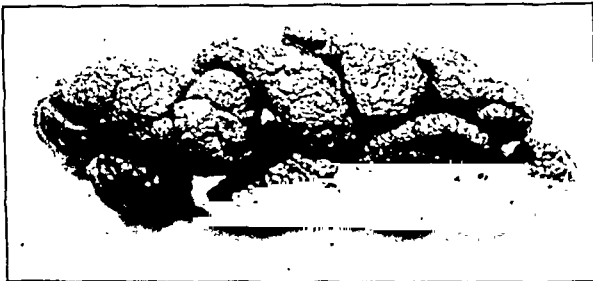


FIG. 2.—The entirely segmented or normal human feces with which the normal intestinal rate is correlated. Together these indices signify complete digestion and absorption ("anabolic nutrition").

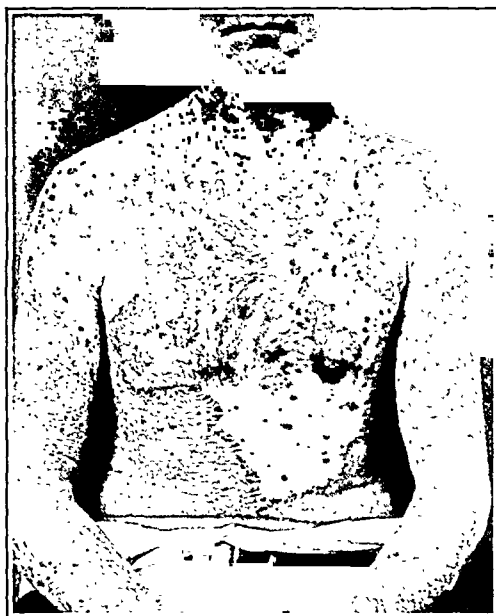


FIG. 3.—The skin of a patient with severe psoriasis.

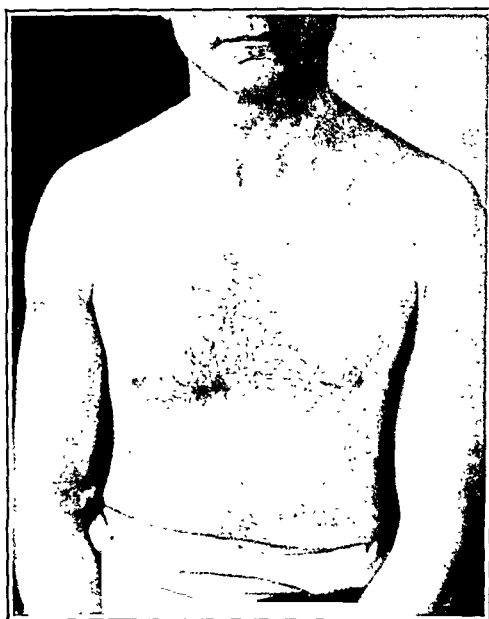


FIG. 4.—The regenerated and healthy skin of the same patient after many months of anabolic nutrition from the correction of erroneous ways of eating.

patients are educated to eat and live in order so to operate the proximal colon that entirely segmented feces and normal intestinal rates are produced. Also, as the digestive fluids are likely to be impotent in these deficient patients, the administration of dilute hydrochloric acid (U.S.P.), gastric enzymes, and enteric-coated pancreatic preparations may be beneficial. Injections of insulin in abnormally lean patients are sometimes helpful. Finally, as it takes months and years of anabolic nutrition to overcome the very deficient condition in these patients, constant encouragement to progress from a state of chronic invalidism and to become more active is very essential. Indeed, this psychologic form of treatment is so important that other forms of therapy, if they do not interfere with the nutrition, may be applied to some patients with profit.

To find out the causes of malabsorption, a detailed inquiry into patients' ways of eating and living is made. Of 30 patients questioned in this way, 19 were found to eat too fast; 17 took laxatives, oil, or enemata regularly; 10 habitually ate cakes, crackers, fruit or candy between meals or before going to bed; 5 ate dinner at noon; 8 ate an excess of breads, cakes, crackers, and other cereal foods; 6 consumed too much protein food; 5 were too fond of fat food; and 19 had an irritable colon and rapid intestinal rate from too much fruit, especially oranges and grapefruit. And most of them ate insufficient vegetables. These erroneous ways of eating caused diarrhea or soft stools; but very obvious signs of indigestion were often revealed by the chemical and microscopic examination of patients' feces. In these tests, poor fat digestion was the most common, starch the next, and protein the least. Some of the stools had an acid reaction to litmus, which was changed to alkaline by treatment. Details of these and other changes in the colonic contents from the correction of erroneous ways of eating are shown in Table 1.

To create anabolic nutrition, patients are taught, from illustrations of the segmented, formed and soft types of the feces and from diagrams and roentgenograms of colonic action, the relation of the fecal specimens and colonic functions to the operations of the nutritive apparatus. They are also given printed outlines which describe the purpose and amplify the directions of the treatment and are shown a form to follow in keeping a record of nutrition. At the top of these records, preliminary directions, such as "eat slowly and only at meal times," and other health measures are written out. Patients then record the food, beverages (except water) and medicines ingested, the time spent at meals, the time and kind of dejections, and determinations of the intestinal rate for a week, and then return with records. Part of a patient's first record of nutrition is often similar to Record 1.

TABLE 1.—THE CHANGE PRODUCED BY ANABOLIC NUTRITION IN THE INTESTINAL RATE, FORM AND REACTION OF THE FECES, AND THE DIGESTION OF A FEW PATIENTS.

Initials of patient.	Dates of examination.	Intestinal rates in hours. *Without laxatives.	Examination of feces.				
			Form.	Reaction to litmus.	Protein.	Digestion of Fat.	Starch.
B. B. A.	9/30/31 10/14/31	13-85 34-108	Soft Formed	Acid Alkaline	Fair Good	Poor Poor	V. poor Poor
L. G. B.	10/24/31 12/15/31	14-60* 37-108	Soft Formed	Alkaline Alkaline	Good Good	Poor Fair	V. poor Fair
M. B. C.	3/19/30 12/14/30 6/30/31	14-108* 63-134 36-86	Soft Normal Formed	Acid Neutral Alkaline	Fair Good Fair	Poor Fair Fair	Fair Fair Poor
G. S. C.	12/4/30 1/5/31 5/4/31 11/9/31	12-42 19-67 14-87 37-135	Soft Formed Formed Normal	Acid Neutral Alkaline Alkaline	Fair Good Good Good	Poor Fair Fair Fair	Fair Poor Poor Fair
A. M. C.	7/21/31 8/11/31 1/13/32	36-63* 62-86 39-135	Soft Soft Formed	Alkaline Alkaline Alkaline	Good Good Good	Poor Poor Poor	V. poor Fair Fair
A. C.	3/3/30 11/6/30	63-109 38-110	Soft Formed	Acid Neutral	Good Good	Poor Fair	Fair Fair
C. H. F.	6/29/31 12/14/31	45-85 43-119	Formed Formed	Alkaline Alkaline	Good Good	Fair Fair	Poor Poor
I. C. H.	12/10/29 3/ 7/30 5/16/30 10/22/30	14-62* 20-74 45-156 37-132	Soft Soft Normal Normal	Acid Neutral Alkaline Alkaline	Fair Good Good Good	V. poor Fair Good Fair	Poor Poor Fair Fair
G. L.	1/15/30 2/ 6/30 12/27/30	26-50 36-110 36-110	Soft Formed Formed	Neutral Alkaline Alkaline	Good Good Good	Poor Fair Fair	Fair Good Fair
E. L.	8/18/30 9/17/30 11/14/30	13-60 37-85 60-110	Soft Formed Normal	Acid Neutral Alkaline	Fair Good Good	Fair Poor Fair	Poor Fair Good
G. G. M.	12/ 1/30 3/25/31 4/14/31	38-75 15-110 51-108	Soft Soft Formed	Alkaline Alkaline Alkaline	Good Good Good	Poor Fair Fair	Good Good Good
L. A. M.	11/ 3/30 6/15/31	27-86* 38-110	Soft Formed	Acid Alkaline	Fair Good	Poor Poor	Poor Good
G. N.	5/16/30 6/19/30 10/ 6/30	60-134* 63-111 62-116	Formed Formed Normal	Acid Neutral Alkaline	Good Good Good	Good Good Good	Poor Fair Good
A. J. R.	3/14/30 5/29/30 3/13/31	16-110* 39-110 39-205	Formed Formed Normal	Acid Neutral Neutral	Good Good Good	Fair Poor Fair	Poor Fair Fair

RECORD 1.

DOE, DAVID.

HEALTH MEASURES TO IMPROVE: Eat slowly and only at meal times.

Wednesday, October 7, 1931.

6.30 to 6.55 P.M. Lamb, cauliflower, bread and butter, chocolate blanc mange, cookies.

7 P.M. Seeds taken to mark this meal.

Thursday, October 8.

7.15 to 7.30 A.M. Prunes, oatmeal, scrambled eggs and muffins, coffee.

8 A.M. Soft dejection with first seeds. *Initial rate 13 hrs.*

12.30 to 12.45 P.M. Lamb hash, muffins and butter, baked apple, cake.

6.30 to 6.50 P.M. Beef steak, potato, white bread and butter, vanilla ice cream.

9.30 P.M. No dejection.

Friday, October 9.

7.20 to 7.35 A.M. Pears, cream of wheat, eggs and bacon, toast, coffee.

8.25 A.M. Soft dejection with seeds.

12.35 to 12.50 P.M. Veal stew, rye muffins and butter, stewed pears, cake.

6.25 to 6.50 P.M. Haddock, rice, beets, rolls and butter, custard pie.

10.15 P.M. No dejection.

Saturday, October 10.

7.25 to 7.35 A.M. Orange, shredded wheat, mackerel, doughnut, coffee.

8 A.M. Soft dejection with last seeds. *Final rate 61 hrs.*

12.20 to 12.50 P.M. Fish chowder, pilot crackers, peach pie.

6.35 to 7.30 P.M. Celery soup, roast beef, potato, broccoli, rolls and butter, fruit salad, bar-le-duc, cream cheese and crackers, peach ice cream, and cake, coffee.

11.30 P.M. Soft dejection without seeds.

The dejections noted by patients in these first records are often of the soft type; and the "marked" evening meal in passing through the digestive system in 13 (initial) and 61 hrs. (final) signifies a rapid intestinal rate. The former erroneous ways of eating may be largely responsible for the malabsorption, but some foods should be omitted or greatly reduced, to relieve the irritability of the colon. Accordingly, still more health measures are advised, such as "eat many vegetables and sparingly of meats, cereal food and fruit" and are written at the top of a second sheet for a record of nutrition. These measures should be adopted immediately, but records should not be started for a week, in which case another appointment is given in 2 weeks. At this visit, patients generally feel better, and may have lost a few pounds. They are also likely to have noted that some dejections were formed instead of soft and, while the initial intestinal rate may still be rapid, at 14 hrs., the final rate has extended to 85 hrs. These and other changes indicate that better alimentary mixtures have improved the colonic functions (Table 1). At this time, when patients begin to make better use of the food going through them, they may also be advised to eat a small breakfast and lunch.

From now on, patients should be seen every few weeks in order to consider the state of the joints, the general condition, and the weight of the body, but more particularly for the examination of records of nutrition. Unless patients present records showing 1 and sometimes 2 daily dejections of entirely segmented feces and, more

particularly, intestinal rates of about 38 (initial) and 110 hrs. (final) or better, at these visits, they must carry out still more health measures and be seen frequently. However, others who have improved in health, strength and weight, and have normal dejections and, especially, normal rates may be seen less frequently. Whenever these patients are seen they must present a week's record of nutrition, as well as records of bi-monthly determinations of the intestinal rate and bodily weight. Besides examining these records and the condition of the joints, the state of other disorders such as anemia and hypoglycemia may be observed every few months.

To reduce the swelling, alleviate the pain and restore the action of the joints, rest, heat, massage or exercises are most beneficial if supervised by an experienced physiotherapist under a surgeon. This is because the relief of each joint is an individual problem. These measures are best applied in combination, as baking and massage alone are not often effective. The acutely painful and swollen joint must be kept quiet, and the unnecessary use of enlarged knees, wrists or phalangeal joints is likely to increase the discomfort and swelling. To assure proper rest for the vertebræ, braces or collars may be applied. In this stage, too, the use of heat should not be extreme or long continued, and massage or exercises should not be used. With the subsidence of pain and swelling, more extended and intense baking or hot fomentations, and gentle superficial massage above and below the joints may be practised. In this stage, too, patients may be taught to contract gently the muscles which control the joints, in order to improve the tone and condition of the muscles, articular cartilages and bones. If the joints are protected by traction and jointed splints to allow the greatest motion without discomfort, exercises may be tried. All of these measures increase the circulation and thus improve the nutrition of the joint. On the relief of pain and superficial swelling, the joints may be directly and more vigorously massaged, and the muscles which control them extensively exercised; but an increase of swelling is a contraindication to the use of these measures.

The Restoration and Control of Health. The results of an attempt to educate several hundred patients in the creation and control of health by anabolic nutrition to cure arthritis are shown in Table 2.

TABLE 2.—THE RESULTS OF ANABOLIC NUTRITION IN THE TREATMENT OF ARTHRITIS.

Kind.	Number.	Condition.	Number.
<i>Patients.</i>			
Private	74	Healthy	43
Charity	167	Improved	75
	—	Improved after two trials	(7)
Total seen	241	Unimproved or worse	34
Uncoöperative	89		—
	—		152
Total studied	152		

Women outnumbered men two to one; and while most were middle aged, a few were young and some were old. Americans of moderate intelligence predominated; and they were not only interested in new principles of health education but also exercised commendable control in correcting erroneous ways of eating. Some of the patients could not be taught or would not coöperate; and only those who brought in 5 or more records over a period of more than five months have been considered in evaluating the treatment. Of the remainder, more than one-fourth have been cured, because the swelling and pain have been entirely relieved and the motility of the joints has been generally normal. Details of the restoration of health in some of these patients are shown in Table 3. About one-half have improved and enjoy an extended sphere of activity. Some of these patients have not been treated long enough to become healthy. A few of them tried to create anabolic nutrition once, failed and became worse; and then after a while tried again and succeeded. Finally, the remainder has stayed the same or become worse. A few of these patients could not understand the principles of treatment, but most of them would not coöperate. The results obtained in the whole group are encouraging, although the relief of the disease and the prevention of relapses in more patients might have been possible if better instruction and especially a better "follow-up" could have been carried out. Ober¹² has already outlined a plan to control the health of patients with arthritis.

When a state of health is created to cure disease, the fight is *only half won* when arthritis is relieved; for the improved state of well-being must be subsequently controlled if the disease is to be cured. All persons are human and are likely to digress from the even, and sometimes dull, tenor of healthy living. Such digressions, if infrequent and of short duration, may not be injurious if a reserve of health has been established. To prevent another attack, it is necessary to know how well these persons control anabolic nutrition in order to remain healthy. To this end, all those instructed in these principles of treatment are required to observe the dejections and keep them normal; then to make and record tests of the intestinal rate and figures of bodily weight every few weeks; and several times a year, according to the supervision needed, they are requested to bring in records of nutrition. The response to such a request is illustrated in Record 2. At one of these visits, a comprehensive and exact examination of the body, joints and various specimens may be carried out to assure these persons of good health. Details of treatment of a few patients and healthy persons who have endeavored to create and control health by anabolic nutrition are described in the following reports. The minor digressions from right eating or living that produced mal-absorption and made the patients worse are especially interesting and are written in italics.

TABLE 3.—THE RESTORATION AND CONTROL OF HEALTH BY PATIENTS FROM ANABOLIC NUTRITION.

Initials.	Age and sex.	Diagnosis, type and duration of arthritis.	Erroneous ways, excesses, or deficiencies of food consumption.	Condition, weight, feces and intestinal rate during treatment (the 4 items are listed consecutively in each column).			
				First week.	Second month.	Sixth month.	First year.
F. A.	41 F.	Clin., hypert. 10 yrs.	Fruit +, laxatives +	Same, 135 lbs.	Same, 135 lbs.	Improved, 139 lbs.	Well, 138 lbs.
J. M. B.	58 F.	X-ray, hypert. 1 yr.	Irregular +, fruit +	Soft, 12-60 hrs.	Nor., 86-123 hrs.	Nor., 37-144 hrs.	Nor., 38-132 hrs.
R. B.	52 F.	Clin., arth. 2 yrs.	Foods +, fast +, laxatives +	Same, 155 lbs.	Impr., 152 lbs.	Worse, 157 lbs.	Well, 155 lbs.
J. P. B.	38 F.	X-ray, hypert. 8 yrs.	Cereals +, meats +, fast +, vegetables -	Same, 168 lbs.	Formed, 38-120 hrs.	Soft, 13-01 (food + +)	Nor., 39-110 hrs.
D. B.	33 M.	Clin., arth. 21 yrs.	Fast +, sweets +, meats +	Same, 159 lbs.	Same, 174 lbs.	Impr.,
M. C.	36 F.	Clin., arth. 1 yr.	Fast +, food +, laxatives +	Same, 115 lbs.	Soft, .. (food +)	Formed,	Well, 167 lbs.
R. C.	44 F.	X-ray, hypert. 1 yr.	Food -, meat -, laxatives +	Same, 138 lbs.	Impr., 143 hrs.	Impr., 145 lbs.	Nor., 151 lbs.
S. D.	49 F.	X-ray, hypert. 1 yr.	Irregular +, fast +, fruit +, laxatives +	Formed, 94-108 hrs.	Nor., 15-140 hrs.	Nor., 46-97 hrs.	Nor., 60-110 hrs.
M. F.	53 F.	X-ray, hypert. 5 yrs.	Foods +, laxatives +	Same, 165 lbs.	Formed, 38-87 hrs.	Worse, 122 lbs.	Worse, 122 lbs.
I. F.	54 F.	X-ray atrophic 1 yr.	Food +, fast +, irregular +	Same, 146 lbs.	Same, 144 lbs.	Well, 139 lbs.	Soft, 15-87 (fruit +)
F. F.	40 F.	Clin., arth. 1 yr.	Food + cereals +	Formed, 17-126 hrs.	Impr., 150 lbs.	Nor., 109-157 (meat -)	Well, 140 lbs.
E. F.	49 F.	X-ray, atroph. 1 yr.	Fast + cereals +, vegetables -	Soft, 20-38 hrs.	Nor., 39-144 hrs.	Soft, 15-63 (fruit +)	Nor., 109-157 (meat -)
E. H.	54 F.	X-ray, hypert. 7 yrs.	Fast +, irregular +, cereals +, vegetables +	Same, 161 lbs.	Impr., 161 lbs.	Impr., 149 lbs.	Well, 147 lbs.
A. I.	61 F.	Clin., arth. 5 yrs.	Fast +, sweets +, oil +	Same, 134 lbs.	Nor., 36-110 hrs.	Nor., 37-159 hrs.	Nor., 41-113 hrs.
M. McI.	35 F.	Clin., arth. 1 yr.	Fast +, irregular +, cereals +, sweets +	Same, 174 lbs.	Formed, 25-135 hrs.	Impr., 165 lbs.	Well, 145 lbs.
T. O'B.	31 M.	Clin., hypert. 2 yrs.	Fast +, irregular +, fruit +	Formed, 12-134 hrs.	Same, 133 lbs.	Impr., 135 lbs.	Nor., 38-143 hrs.
M. R.	44 F.	Clin., hypert. 3 yrs.	Fast +, irregular +, cereals +, sweets +	Soft, 14-51 hrs.	Same, 164 lbs.	Impr., 162 lbs.	Well, 169 lbs.
W. S.	43 F.	X-ray, hypert. 1 yr.	Fast +, cereals +, meat +, vegetables -	Same, 145 lbs.	Formed, 13-109 hrs.	Nor., 39-135 hrs.	Nor., 13-110 hrs.
E. W.	53 F.	X-ray, atroph. 2 yrs.	Fast +, irregular +, fruit +	Soft, 36-97 hrs.	Impr., 112 lbs.	Formed, 13-110 hrs.	Well, 157 lbs.
C. W.	60 F.	Clin., arth. 12 yrs.	Fruit +, fat +	Same, 154 lbs.	Impr., 162 lbs.	Nor., 39-122 hrs.	Nor., 39-109 hrs.
				Same, 157 lbs.	Formed, 13-110 hrs.	Well, 159 lbs.	Well, 116 lbs.
				Soft, 38-63 hrs.	Nor., 38-131 hrs.	Nor., 39-135 hrs.	Well, 158 lbs.
					Formed, 25-108 hrs.	Nor., 39-120 hrs.	Nor., 39-120 hrs.
					Same, 145 lbs.	Impr., 144 lbs.	Well, 150 lbs.
					Same, 143 lbs.	Nor., 38-133 hrs.	Nor., 61-120 hrs.
					Same, 143 lbs.	Impr., 153 lbs.	Well, 153 lbs.
					Soft, 13-88 (fruit +)	Nor., 40-131 hrs.	Nor., 38-93 hrs.
					Same, 206 lbs.	Impr., 199 lbs.	Well, 183 lbs.
					Soft, 25-117 hrs.	Nor., 41-133 hrs.	Nor., 63-135 hrs.
					Same, 151 lbs.	Impr., 150 lbs.	Well, 141 lbs.
					Formed, 21-112 hrs.	Nor., 39-132 hrs.	Nor., 43-75 hrs.
					Same, 157 lbs.	Impr., 155 lbs.	Well, 150 lbs.
					Nor., 38-110 hrs.	Nor., 14-110 hrs.	Nor.,

RECORD 2.

JONES, JOSEPHINE

HEALTH MEASURES TO CONTINUE: Eat a small breakfast and lunch, sparingly of meat, fat and cereal food, and fruit according to absorption. Determine the intestinal rates and weights in May and June and bring in a complete record in July.

	<i>Rates.</i>	<i>Weights.</i>
May	37 to 132 hrs. and 63 to 134 hrs.	137, 139
June	61 to 120 hrs. and 57 to 156 hrs.	138, 138

Wednesday, June 28, 1931

7 to 7.45 P.M. Cold consommé, cracker, roast chicken, potato, beet greens, tomato and lettuce salad, bar-le-duc cheese and crackers, demi-tasse.
7.45 P.M. Seeds taken to mark this meal.

Thursday, June 29.

8 to 8.10 A.M. Corn muffins and butter, coffee.
9.30 A.M. Normal defecation.
1.30 to 1.50 P.M. Cheese soufflé, asparagus salad, roll and butter, cocoa, cantaloupe melon.
7.05 to 7.30 P.M. Salmon, peas, spinach, bread and butter, raspberry mousse, cake, demi-tasse.

Friday, June 30.

8.10 to 8.25 A.M. Toast and butter, coffee, milk.
10.15 A.M. Normal defecation.
1.15 to 1.40 P.M. Tomato omelette, potato, roll and butter, fruit salad.
7.30 to 8.30 P.M. Cold clam broth, steak, potato, broccoli, roll and butter, asparagus on toast, strawberry ice cream, cake, demi-tasse.
11 P.M. Normal defecation with first seeds. *Initial rate 50 hrs.*

Saturday, July 1.

8.30 to 8.45 A.M. Wheat gems and butter, coffee, milk.
9 A.M. Formed defecation with seeds.
1.30 to 1.35 P.M. Fish chowder, crackers, cup custard.
7 to 7.30 P.M. Duck, jelly, potato, string beans, apricot salad, demi-tasse.
10.30 P.M. No defecation.

Sunday, July 2.

8.30 to 8.45 A.M. Brown bread and butter, coffee.
10.15 A.M. No defecation.
1.45 to 2.05 P.M. Scrambled eggs and bacon, roll and butter, cocoa, asparagus salad, prune whip.
7 to 7.30 P.M. Roast beef, potato, peas, roll and butter, apple pie.
10 P.M. Normal defecation with seeds.

Monday, July 3.

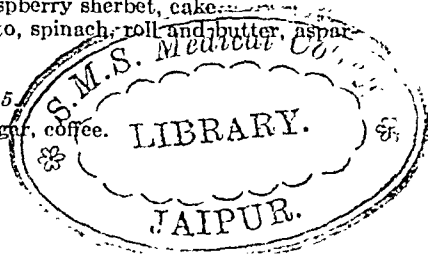
8.30 to 8.45 A.M. Toast and marmalade, coffee, milk.
9.45 A.M. Normal defecation with seeds.
1 to 1.20 P.M. Bouillon, welsh rarebit, spinach, strawberries and cream, cake.
7 to 7.30 P.M. Lamb, potato, cauliflower, roll and butter, rennet, pear, demi-tasse.
10.30 P.M. Small normal defecation with seeds.

Tuesday, July 4.

8 to 8.30 A.M. Corn muffins and butter, coffee.
10 A.M. Normal defecation with last seeds. *Final rate 134 hrs.*
1.30 to 1.45 P.M. Shirred egg, peas, roll, milk, raspberry sherbet, cake.
7 to 7.30 P.M. Cold consommé, lamb chop, potato, spinach, roll and butter, asparagus on toast, peach ice cream, demi-tasse.

Wednesday, July 5.

8.10 to 8.20 A.M. Puffed wheat with milk and sugar, coffee.
10.30 A.M. Normal defecation without seeds.



CASE 1.—Mr. A. M. C., American, aged 45, married, salesman, has had pain in the spine and pain and swelling of the wrists for 2 years. Roentgen ray diagnosis, hypertrophic arthritis. Several years ago used to eat too much and too fast, an excess of sweet and cereal food, and weighed 175 pounds. Has taken laxatives regularly for many years. Weight now 135 pounds. Indigestion and malnutrition shown by soft, alkaline feces, in which protein digestion is fair, fat poor, and starch very poor.

July 21, 1931. Advised to omit laxatives, eat slowly, fruit at lunch and dinner, and try to deject twice daily. Also to rest, use hot soaks t. i. d. and take acetylsalicylic acid p. r. n.

July 28, 1931. Weight 132½ pounds. Regular without laxatives during the week, but has had soft dejections and a rate of 36 and 63 hrs. To eat less fruit.

August 11. Feels stronger and sleeps better. Weight reduced to 131½ pounds. Dejections generally regular and formed, with a rate of 62 to 86 hrs. Good diet.

September 1. Less swelling and pain in joints. Weight 131 pounds. Dejections regular and normal, rate 62 to 135 hrs. To eat many vegetables.

October 11. Back at work again and travelling about. Swelling and pain increased from *too much use of limbs*. Weight 130 pounds. Rate of 63 and 87 hrs. To eat slowly, less fruit, but according to absorption. Also to get more rest and take digestive tablets.

December 1. Continues to have pain but swelling is reduced; also sleeps soundly and weight is increased to 134 pounds. Rate 63 and 111 hrs. Good diet.

March 7, 1932. *Ate some decomposed food*, had diarrhea for a week, lost weight, and had a return of pain and swelling. Rates in February 41 to 107 and 63 to 136 hrs. To eat sparingly of fat food and fruit according to absorption.

May 21. Has had an opportunity to rest more recently, pain and swelling have subsided and weight is 132 pounds. Rate 63 to 132 hrs. To continue rest and same diet.

August 4. Improvement continues and weight continues at 132. Rate in June 64 to 133, July 63 to 134 hrs. Now dejections are generally formed and normal and rate is 63 to 110 hrs.

CASE 2.—Mrs. G. N., American, aged 46, housewife, has had pain and swelling of hands and knees for 10 years. Roentgen ray diagnosis, hypertrophic arthritis. Weight 145 pounds. Used to eat frequently between meals, and especially of sweet stuff. Now eats too much meat, bread and fat food, and too few vegetables. Indigestion shown by formed, acid feces, in which protein and fat digestion are fair, but starch digestion is poor.

May 15, 1930. Advised to reduce protein, fat and cereal food, and eat more vegetables.

May 22. About the same. Dejections irregular, with a rate of 60 to 134 hrs. Weight 145 pounds. Is eating too much cereal food and too few green vegetables.

June 19. About the same, but is sleeping better. Weight 144 pounds. Dejections still somewhat irregular and formed, with a rate of 63 to 111 hrs. Eat a light breakfast and lunch, less meat and fish, and fruit according to absorption.

September 4. While abroad, *ate irregularly*, had regular but soft dejections. Rate not determined. Pain and swelling became worse. Weight 145 pounds. Since returning, has returned to diet and dejections have become irregular but normal, rate 70 to 165 hrs. To eat more fruit but according to absorption.

October 6. Improved, swelling reduced and pain much relieved. Weight 144 pounds. Dejections regular and normal again, with a rate of 62 to

116 hrs. In a health test the physical examination was negative, and blood pressure 113/80. In laboratory tests the hemoglobin was 72% (Newcomer); corpuscle count, 4,200,000; leukocyte count, 8600; differential count: polymorphonuclears, 65%; lymphocytes, 26%; myelocytes, 0%; endothelials, 7%; eosinophils and basophils, 2%. Non-protein nitrogen, 32 mg. and sugar, 123 mg. Feces normal, alkaline, protein digestion good, fat good, starch fair. Urine normal.

January 8, 1931. Much improved, pain and swelling about gone. Weight 145 pounds. Had a cold recently, took laxatives and enemata and had irregular, soft dejections for a while. After dejections became normal they were regular, with a rate of 63 to 156 hrs. To eat a light breakfast and lunch, many green vegetables and more fruit, but according to absorption.

March 5. About well, gets about as she wishes without pain, and swelling about gone. Weight increased to 148 pounds. Dejections regular and normal, rate 63 to 111 hrs. To eat very sparingly of cereal and fat food. September 18. Well. Weight 147 pounds. Rate 62 to 132 hrs.

CASE 3.—Mrs. G. S. C., American, aged 52, housewife, has had pain and swelling of the neck, shoulders and knees for 10 years, and Roentgen ray diagnosis of hypertrophic arthritis. Weight now 139 pounds. Eats irregularly, too much cereal food especially, and takes laxatives regularly. Indigestion and malnutrition shown in first naturally dejected stool by soft, strongly acid feces, a fair protein digestion, but a poor fat, and very poor starch digestion.

November 27, 1930. Advised to eat slowly, only at meals, a small breakfast and lunch; to omit oranges and grapefruit but eat other fruit at lunch, and try to deject twice. Rest advised, and also acetylsalicylic acid p. r. n. Physiotherapy advised.

December 4. During the week the condition has remained unchanged and weight is 139 pounds. Dejections regular but soft, with a rate of 12 to 42 hrs. A reduction of cereal, fat and sweet food advised.

January 5, 1931. Still has pain and swelling of the joints and weight is unchanged at 139 pounds. Feces formed at times, with a rate of 19 to 87 hrs. Eats too much cereal food and too few green vegetables especially.

March 9. Began to improve, went on a visit, *ate irregularly and too much rich food* and became worse. Dejections regular, but soft, with a rate of 14 to 39 hrs. To eat only at meals, a light breakfast and lunch, many leafy vegetables, and fruit according to absorption.

June 9. Continues to improve, has less pain, and swelling of joints had entirely subsided. Gets about comfortably. Weight 144 pounds. Dejections regular, generally formed, alkaline, with a rate of 46 to 133 hrs. To eat sparingly of fat and starchy food.

September 9. Has gained in health, but has been *eating irregularly and too much cereal food lately*. Had a fair rate of 12 to 113 hrs. in August, but recently has had many soft dejections and a rate of 36 to 63 hrs. Advised to eat only at meals and less cereal food.

November 9. Much improved again. Weight reduced to 142, dejections regular and often normal, with a rate of 37 to 135 hrs.

March 16, 1932. Continued to improve up to a month ago, when dejections became soft, with a rate of 15 to 61 hrs. There has been a slight return of pain and swelling. Weight reduced to 136 pounds. Record shows ingestion of *too much rich food and cereal food*.

December 7. Is slowly becoming better nourished and healthier. Weight increased to 139 pounds. Has had formed and normal dejections generally and rates of about 63 to 134 hrs. Now brings in a record of 18 to 111 hrs. To eat less fat and cereal food, more green vegetables, and less fruit but according to absorption.

February 27, 1933. Has made a marked improvement. Weight reduced to 135 pounds. Has had normal dejections generally, and on tests of the rate every few weeks has generally had rates of about 63 to 134 hrs. Brings in a record with regular and normal dejections and a rate of 87 to 164 hrs. To eat more fruit especially, but according to absorption.

CASE 4.—Miss E. W., American, aged 53, has had pain and swelling of the knees for 2 years. Roentgen ray diagnosis, atrophic arthritis. Weight 154 pounds. Now eats too fast, irregularly, and too much fruit.

October 31, 1929. Advised to eat a small breakfast and lunch, but a substantial dinner at night. Also to omit oranges and grapefruit and eat other fruit at lunch only.

November 6. About the same, weight reduced to 150 pounds. Dejections formed, with a rate of 15 to 135 hrs. To eat less cereal food.

December 18. Condition improved. Weight 148 pounds. Rate 36 to 156 hrs. Good diet.

February 12, 1930. Continues to improve. Weight 147 pounds. Rate 40 to 156 hrs.

July 2. *Well*. Weight 142 pounds. Rate 39 to 110 hrs.

December 10. Continues *well*. Weight 146 pounds. Rate 38 to 110 hrs. Good diet.

April 15, 1931. Continues *well*. Weight 149 pounds. Rate 39 to 111 hrs.

October 14. Continues *well*. Weight 149 pounds. Rate 41 to 113 hrs.

February 17, 1932. Continues *well*. Weight 149 pounds, and has had rates of 39 to 111, 39 to 113, 39 to 111 hrs.

November 30. Continues *well*. Weight 145 pounds, and has had rates of 41 to 112, 40 to 111, 41 to 113 hrs.

March 29, 1933. Continues *well*. Weight 145 pounds. Rate 39 to 123 hrs.

The Operation of the Proximal Colon. "The wonder is not that structural imperfections and functional disharmonies should develop in proportion to our numbers, but rather that so many of us escape harm altogether and enjoy good health. . . . The solution of our problem of life is a fuller knowledge of the use and working of those parts of our bodies most apt to give way under our modern ways of living—the use of such structures as the great bowel. And when we have replaced our ignorance by real knowledge we shall be in a position not to adapt our bodily structures to our mode of living, but our mode of living to our bodily structures. . . . The bowel is not a useless or superfluous organ, but one which we in our ignorance are maltreating." (Keith.¹³)

To adapt our ways of eating and mode of living to the complex and delicately adjusted control exercised by the proximal colon, certain requirements must be fulfilled. To this end, the food ingested by a healthy person may be somewhat similar to that in Record 2. One requirement for this action is the consumption of a small amount of food at breakfast and lunch but a substantial amount at dinner; although a small combined breakfast-lunch in the middle of the morning and a substantial dinner in the evening is advisable for obese and sedentary patients. On the contrary, the consumption of insufficient food does not appear to supply the needs of the tissues for nourishment and leave a residue for daily

defecation; thus the dejections are irregular, the intestinal rate abnormally extended, and the patient malnourished. The weight and value of the food may vary from 50 to 100 gm. of protein, 50 to 100 gm. of fat, and 150 to 200 gm. of carbohydrate (1500 to 2500 large calories), according to the age, sex, size and activity of the person. While the amount of food is small, if the intestinal rate is normal there is a large amount of nutritive material in the digestive system. Everyone is instructed to attempt defecation an hour or two after breakfast and again at bedtime, irrespective of an impulse. One and occasionally 2 days without a defecation improve the absorption if the intestinal rate has been too rapid. A second requirement is the thorough mastication of the food; each mouthful of starchy food especially should be made fluid with saliva before it is swallowed. A third requirement is that the diet be "complete," as avitaminosis sometimes causes diarrhea.¹⁴ A fourth requirement is that many vegetables be ingested to make the aliment alkaline. Forman, Pennington and Funkhouser¹⁵ found the soft feces often had an acid reaction of pH 5 to pH 6.5; whereas the segmented stool had an alkaline reaction of pH 7 to pH 7.5. A fifth requirement is to eat fruit according to absorption. As the action of the colon is not known until after the defecation, which generally occurs after breakfast, the ingestion of fruit is advised at lunch and sometimes dinner. Some patients get an irritable colon from the ingestion of too much fruit, especially the citrous fruits; whereas, when the irritability of the colon has been relieved, enough fruit must be ingested to produce regular defecation and prevent the intestinal rate from becoming abnormally extended. A sixth requirement is the omission of all laxatives, oils or enemata; because regular and normal dejections are produced by the regulation of normal foods.¹⁶ Furthermore, Magnus¹⁷ has observed that the normal antiperistaltic waves of the proximal colon in animals are inhibited by food containing senna.

Two glasses of water or a corresponding amount of fluid are advised at each meal, one on arising and one at bedtime, under ordinary conditions. Moderation in the use of beverages and malted or spirituous liquor and tobacco does not appear injurious. Finally, 8 hrs. of sleep are advocated, and this is often accomplished if some physical exercise is taken outdoors every day. Exercise is greatly restricted in extremely deficient patients, however, as the intestinal rate is likely to be rapid; and these patients are advised to rest once or twice during the day and try to sleep more than 8 hrs. at night.

The Wisdom of the Body, the Conscious Colon, and Health. " . . . The circuit of the blood is accomplished, now more rapidly, now more slowly, according to the temperament, age, etc., of the individual, to external and internal circumstances, to naturals and non-naturals—sleep, rest, food, exercise, affections of the mind and the

like.” . . . through the wisdom of the body “The heart has a marvelous power of adapting its work and its performance to the needs of the body.” (Starling.¹⁸)

Just as the circulation changes according to sleep, rest, food, exercise and affections of the mind and the like, so the cycle of digestion and absorption of the aliment, regulated by the same kind of “wisdom of the body,” likewise varies according to our ways of eating and living. Then again, as the heart adapts its work to the needs of the body, so does the digestive system adapt its performance to the requirements of the tissues for nutrient substances. In this way the functions of the digestive system operate as a perfect nutritive apparatus, in which the course of the aliment is largely controlled by stimuli within and without on the dual and conscious action of the digestive pouches. Thus the primary pouch—the stomach—automatically acts and reacts according to the ingested mixture. For proper food is normally churned with the digestive fluids to promote mixing and digestion; but an extremely unsuitable mixture is abnormally expelled, by vomiting, to prevent the absorption of injurious substances. Moreover, the secondary pouch—the proximal colon—acts in a similar way; for here, in animals, the aliment is normally worked over by waves of peristalsis and anti-peristalsis, and then “a segment from its contents is every now and then nipped off by a ring of constriction, and carried away to be moulded in its further passage down the colon to the firm fecal nodule.”¹⁹ But a rapid and propulsive passage of the contents which results in diarrhea, and one probably due to irritant products, has also been observed.²⁰ In man, too, the aliment is passed through the colon by two kinds of action. One is the movement of Fischl and Porges,²¹ by which small, uniform segments are passed slowly through the distal colon. This act, similar to the normal action in animals, evidently signifies the normal action of the colon. The other is the mass movement of Holzkecht,²² by which large, irregular masses are rapidly passed through the colon. This rapid propulsive act may be regarded as resembling vomiting, and obviously abnormal. Each function molds the colonic contents in a significant way; for from right eating and living one function produces the entirely segmented feces, and from erroneous ways another action molds the soft and formless stools.

From this point of view the colon operates with a conscious capacity and may be made to serve as an exact and delicately adjusted control, especially of proper ways of eating. Moreover, through “the wisdom of the body” and the “consciousness” of the colon, the soft feces serve as a definite means to determine intestinal indigestion as an early and slight disorder of the nutritive apparatus.⁴ On the other hand, the entirely segmented feces produced by the correction of erroneous ways of eating indicate that the aliment has completed its cycle of digestion and absorption. Thus a morbid

process is replaced by a vital process for the creation of a heretofore unrecognized condition of the human body—an exact state of health from anabolic nutrition.

Summary. A failure of nutrient substances' to construct healthy bone and cartilage, or a metabolic disorder, has often been considered as the cause of arthritis. In many ways health is a vague and variable condition; but from the operation of the digestive system as a perfect nutritive apparatus, through an understanding of the wisdom of the body, a process evidently becomes effective which creates an exact state of health. Such a process is produced by the correction of erroneous ways of eating and living, to operate properly the "secondary digestive pouch," the proximal colon; for this function finally molds the intestinal contents into the uniform masses of the entirely segmented or normal feces and produces normal intestinal rates. As these indices signify complete digestion and absorption, any other kinds of feces or rates are an indication of the passage of nutritive material through instead of into the body and of intestinal indigestion. As the normal indices imply the assimilation of improved nutrient substances by cells, the process created by their production has been called "anabolic nutrition."

In an attempt to create anabolic nutrition to cure arthritis, several hundred patients have been educated; but as a third of them would not coöperate, the value of the treatment is based in this study on 152 patients. Of this number, health has been restored in more than one-fourth, improved in one-half, and remained the same or became worse in the others. In some of those who improved, health is likely to be restored by more prolonged treatment; in a few, one attempt to create anabolic nutrition failed and they became worse, but later another attempt proved beneficial. In those who remained the same or become worse, either an understanding of the principles or coöperation could not be secured. For healthy persons relieved of arthritis to prevent a recurrence, they must be supervised; and therefore they are required to make and record tests of the intestinal rate and bodily weight every few weeks and return to the office or health class with records of nutrition every few months. Thus they may control health by anabolic nutrition, and cure arthritis.

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A SURVEY OF HUMAN INTESTINAL PROTOZOAN PARASITES IN PHILADELPHIA.

BY H. CORWIN HINSHAW, PH.D., M.D.,

FELLOW IN MEDICINE, MAYO FOUNDATION; FORMERLY ASSOCIATE PROFESSOR OF PARASITOLOGY, AMERICAN UNIVERSITY OF BEIRUT, BEIRUT, LEBANON REPUBLIC
(SYRIA),

AND

ETHEL M. SHOWERS, R.N.,
PHILADELPHIA, PA.

(From the Gastro-intestinal Section of the Medical Clinic, University of Pennsylvania Hospital.)

RELATIVELY little information is available as to the frequency and importance of infestation with intestinal protozoa among residents of temperate climates who dwell at home under the conditions of modern city life. It is well recognized, however, that such infestations are significantly frequent in southern sections of the United States and in warmer climates throughout the world; also, that they are exceedingly common in the stools of individuals who are living in large groups such as armies¹ or institutions,² and in those who lack the advantages of modern city sanitation.³ Andrews and Paulson,⁴ in 1931, were able to find *Endamæba histolytica* in only 0.3% of a group of 312 individuals living under modern home conditions in Baltimore. This is in striking contrast to the findings of 67% in a group of 91 soldiers by Kofoed and Swezy,⁵ and of 11.4% in the rural districts of Tennessee by Meleney, Bishop and Leathers,³ and to the estimate of Craig⁶ that between 5 and 10% of the entire population of the United States carry this potentially dangerous parasite.

It is possible that some surveys have been made during periods of silent epidemics, it is probable that the incidence of cases varies from time to time in the same locality, and it is certain that the facilities for transmission vary widely in different strata of the population. The greater ease of obtaining material from institutionalized

groups has led to a disproportionate study of such groups. The recent widespread epidemic traced to Chicago emphasizes the fact that there is a constant potential menace whenever and wherever individuals congregate. The present survey, made during the winter of 1932-1933 and just preceding the Chicago epidemic, demonstrates that other cities as well possess an adequate number of carriers to effect an equal dissemination if facilities are offered. Public health practices should be amended to insure the destruction of ameba cysts along with the much less resistant pathogenic bacteria.

The present investigation was undertaken to learn how frequently intestinal protozoa should be anticipated in this locality among patients entering the medical wards of a hospital. We know of no similar survey of Philadelphia or its immediate vicinity. Interest is added by comparison of these findings with those obtained by one of us (Hinshaw, to be published) in a similar but more extensive survey in the subtropical climate and oriental living conditions of Beirut, Lebanon Republic, Syria.

Material and Methods. Specimens were requested of unselected patients upon admission to the wards of the Medical Clinic of this hospital, regardless of the nature of their complaints. Additional specimens were submitted from patients in whom intestinal disease was suspected, including especially outpatients visiting the gastro-intestinal section: none of these, however, carried *E. histolytica*, so that this departure from our original plan of studying an unselected group had no effect in increasing the incidence of this infestation.

Specimens (535) were examined from 368 patients (average 1.5). The frequent use of mineral oil to avoid constipation in hospital patients often made subsequent specimens unsuitable for study. Among those yielding no intestinal protozoa an average of 1.2 specimens per patient were studied, while for those found to have some kind of infestation 2.1 specimens per individual were secured. Part of this difference is accounted for by the increased interest of the clinicians in the latter group. Study of the tabulations in this paper demonstrates, as has been pointed out before, that with successive specimens from a single patient there is a tendency to discover a larger variety of organisms. It has been estimated that only one-third to one-half of existing infestations are revealed by a single stool examination: their identification may be increased to 80% or better by the proper study of 4 to 6 formed specimens or by the examination of 2 or 3 stools secured after the use of a saline laxative.

The search for motile amebæ requires an arrangement by which the patient can defecate in the laboratory and the specimen be examined immediately; also such study is subject to considerable error in that the motile forms possess less definite features for identification and in that they require more skill and experience for their interpretation. Furthermore, they require the constant presence in

the laboratory of an experienced parasitologist and yield no permanent preparation which can be studied subsequently. For these reasons we chose to base our survey on a study of the encysted forms in stained smears.

The specimens were usually obtained without a cathartic, and specimens following the administration of oily laxatives were always discarded. Although the smears were made as promptly as possible, usually within $\frac{1}{2}$ hr. after defecation, such prompt examination of formed stools for the cysts is not essential. Elsewhere we have frequently examined stools which were mailed from considerable distances. We have also sent stools by air mail from Beirut, Syria, to Hoechst, Germany, where the viability of the cysts was proven by the successful infection of dogs after a transit of over 2000 miles.

Flagellates are much more conspicuous in the active motile state than when stained, being readily overlooked in the latter condition. Their specific identification, however, may be easier when they are stained.

Magath and Ward⁷ carefully compared several methods of examining for intestinal protozoa, and expressed a preference for the study of fresh preparations of liquid stools obtained after a saline purge. Their facilities and skill, however, cannot be duplicated in the average instance, and for such a study as we have made, under ordinary conditions in a large general hospital, we believe that the staining method will yield more dependable results.

Method. Smears of saline emulsions of feces were made on flamed clean slides with a mucilage brush and fixed immediately while moist in hot (60° C) Schaudinn's fluid, in which they remained for 15 min. They were then placed for 10 min. each in 50 and 70% alcohol, strongly colored with iodine. Hydration was accomplished by passage through 50 and 30% alcohol and distilled water. The smears were then mordanted for 10 to 20 min. in a 2% solution of iron alum held at 30–40° C, rinsed in distilled water and stained in a ripened 0.5% solution of hematoxylin for a similar length of time at a similar temperature. Differentiation was carried out under the microscope in a 1% solution of iron alum. The slides were next thoroughly washed in running water for 20 to 30 min. and dehydrated by passage through 30, 50, 70, 90, 95 and 100% alcohol, each for about 5 min.; then left in xylol for 5 min. and mounted in balsam, using a thin coverglass. The smears were systematically searched through an oil-immersion lens.

Results. *Endamoeba histolytica* is the only ameba of man the pathogenicity of which has been proved, and it is, therefore, of the greatest clinical interest. Its presence is at least potentially dangerous both to the individual and to his associates. Only 1 of our patients was suffering from amebic dysentery, while in the others no clear association could be made out between the presence of the parasites and the patient's symptoms. In this paper we are not attempting an

evaluation of the clinical significance of the organism concerned. It was found in 4 of the 368 patients studied. In 2 of them no other parasites were found; in 1 *Endolimax nana* was associated and in the other, *Giardia intestinalis*, *Endamæba tenuis*, and *E. nana* were also present. Three of the 4 cases were diagnosed by the finding of typical cysts of *E. histolytica*. The remaining case exhibited only motile amebæ and their identity was clearly established by their appearance and activity, their ingestion of numerous erythrocytes, and their great concentration in the ulcers of the rectum and sigmoid, which were visualized through the sigmoidoscope. Scrapings from the margins of these ulcers yielded great numbers of the typical amebæ. Specific therapy (emetin-bismuth-iodid) resulted in prompt and total relief of the dysentery. Numerous Charcot-Leyden crystals also were present in these specimens.

We do not believe that it is always possible to identify with certainty large motile amebæ found in stools, especially if the specimen be cold, with impaired motility and scarcity of organisms. Three such cases must be recorded in this series in which the specific differentiation between *E. histolytica* and *E. coli* could not be safely made and additional specimens were unfortunately impossible to secure. In each of these cases we were of the opinion that they were probably *E. histolytica*.

Endamæba coli was found in 18 patients, from whom a total of 33 specimens were studied. We have grouped the classical cysts together with those forms described by Kofoed and Swezy⁸ as *Councilmania lafleuri*. We have never found a case demonstrating the classical forms which did not also yield the *C. lafleuri* types on further study, and all intermediate forms have been frequently observed in this and in other more extensive studies. The association of *E. coli* with other organisms is represented in the following table:

TABLE 1.—INCIDENCE OF *E. COLI* IN STOOLS.

	No. cases.	No. specimens.
<i>E. coli</i> alone	6	6
<i>E. coli</i> and Blastocystis	1	1
<i>E. coli</i> and <i>Endolimax nana</i>	2	2
<i>E. coli</i> , <i>E. nana</i> and Blastocystis	6	14
<i>E. coli</i> , Trichomonas and Blastocystis	1	6
<i>E. coli</i> , Chilomastix and Blastocystis	1	1
<i>E. coli</i> , <i>Giardia</i> , <i>Iodameba</i> and <i>E. nana</i>	1	3
Total occurrence of <i>E. coli</i>	18	33

The incidence of infection in the total group of patients was 4.9%.

Endolimax nana, a small and inconspicuous ameba of man, was the most frequently encountered of all. We have recorded it 131 times in 64 patients. Its association with other organisms is indicated in Table 2, p. 112.

TABLE 2.—INCIDENCE OF *E. NANA*.

	No. cases.	No. specimens.
<i>E. nana</i> alone	9	14
<i>E. nana</i> and <i>Blastocystis</i>	28	52
<i>E. nana</i> and <i>E. tenuis</i>	6	8
<i>E. nana</i> , <i>E. tenuis</i> , and <i>Blastocystis</i>	4	9
<i>E. nana</i> , <i>E. tenuis</i> , <i>Giardia</i> and <i>Blastocystis</i>	2	12
<i>E. nana</i> , <i>E. tenuis</i> , <i>Iodameba</i> and <i>Blastocystis</i>	1	1
<i>E. nana</i> and <i>Iodameba</i>	1	3
<i>E. nana</i> , <i>Iodameba</i> , <i>E. coli</i> and <i>Giardia</i>	1	3
<i>E. nana</i> and <i>E. coli</i>	2	2
<i>E. nana</i> , <i>E. coli</i> and <i>Blastocystis</i>	6	14
<i>E. nana</i> <i>Trichomonas</i> and <i>Blastocystis</i>	1	2
<i>E. nana</i> and <i>E. histolytica</i>	2	10
<i>E. nana</i> and unidentified motile ameba	1	1
Total occurrence of <i>E. nana</i>	64	131

The incidence of infection was 17.4 %.

Endamæba tenuis is one of the most frequently encountered amebæ of man but is usually not distinguished from *Endolimax nana* which it resembles in shape and staining qualities and to which it may be intimately related. Although its specific distinction is not widely accepted we are tentatively recognizing it and separating it from *E. nana* in this study. It was first described by Kuenen and Swellengrebel,⁹ and has been confused with the smaller races of *E. histolytica*.¹⁰ Its importance has been noted by Kofoed¹¹ and placed in the genus *Councilmania*. It is distinctly larger than *E. nana* and its nuclear structure is different with a smaller more centrally placed karyosome. Intermediate forms between the two types are lacking in our material and this constitutes our principal reason for classifying them separately. It must be admitted that differences of technique might be adequate to account for many distinctions in morphology. As experience is added, our distrust of purely morphologic criteria grows. Although *E. tenuis* was associated with *E. nana* in one-half of the cases we cannot accept this as evidence of genetic relationship because the same association is seen between *E. coli* and *E. nana*, or between *Blastocystis* and *E. nana*. The following table shows its association with other organisms:

TABLE 3.—INCIDENCE OF *E. TENUIS*.

	No. cases.	No. specimens.
<i>E. tenuis</i> alone	7	10
<i>E. tenuis</i> and <i>Blastocystis</i>	5	6
<i>E. tenuis</i> and <i>E. nana</i>	6	8
<i>E. tenuis</i> , <i>E. nana</i> and <i>Blastocystis</i>	4	9
<i>E. tenuis</i> , <i>E. nana</i> , <i>Giardia</i> and <i>Blastocystis</i>	2	12
<i>E. tenuis</i> , <i>E. nana</i> , <i>Iodameba</i> and <i>Blastocystis</i>	1	1
<i>E. tenuis</i> and <i>Chilomastix</i>	1	1
Total occurrence of <i>E. tenuis</i>	26	47

The incidence of infection was 7 %.

TABLE 4.—INCIDENCE OF *IODAMEBA BÜTSCHLI*.

	No. cases.	No. specimens.
<i>Iodameba bütschli</i> alone	1	1
<i>I. bütschli</i> and <i>E. nana</i>	1	3
<i>I. bütschli</i> , <i>E. coli</i> , <i>Giardia</i> and <i>E. nana</i>	1	3
<i>I. bütschli</i> , <i>E. tenuis</i> , <i>E. nana</i> and <i>Blastocystis</i>	1	1
	—	—
Total occurrence of <i>I. bütschli</i>	4	8
Incidence of infection 1.1 %.		

Dientamæba fragilis, a rare organism, was found in 2 specimens from 1 patient.

Giardia intestinalis was found 28 times in 9 different patients. It is the only commonly encountered flagellate which is conspicuous and readily found in stained smears. In none of our patients could symptoms be attributable to the infestation. One patient with a roentgenologic diagnosis of duodenitis had enormous numbers of the parasite in duodenal drainage material. Its normal habitat is in the duodenum, appearing in the stools in the encysted state usually, except in diarrhea when it is more likely to appear in the vegetative state. The following table shows its association with other intestinal protozoa:

TABLE 5.—INCIDENCE OF *GIARDIA INTESTINALIS*.

	No. cases.	No. specimens.
<i>Giardia</i> alone	2	2
<i>Giardia</i> and <i>Blastocystis</i>	5	16
<i>Giardia</i> , <i>E. histolytica</i> , <i>E. nana</i> and <i>Blastocystis</i>	1	7
<i>Giardia</i> , <i>Iodameba</i> , <i>E. nana</i> and <i>E. coli</i>	1	3
	—	—
Total occurrence of <i>Giardia</i>	9	28
Incidence of infection: 2.4 %.		

Trichomonas hominis and *Chilomastix mesnili* are usually much more conspicuous in the fresh motile state than in stained material, where, if not numerous, they may be overlooked by the best observers. This report is based upon stained slides and therefore gives an apparent incidence of infection which is probably below the actual figure. They are usually more numerous in liquid stools, especially in diarrhea, but no etiologic significance has been demonstrated.

The flagella of *Trichomonas* and *Chilomastix* are not conspicuous by our method of staining, so that recognition must depend upon the finding of oval or pyriform bodies with inconspicuous nuclei and at least traces of the intracytoplasmic portion of the flagellar apparatus. *Trichomonas* is most readily confused with intestinal yeasts, especially if the staining be too dark. *Chilomastix* has a larger and more vesicular nucleus more anteriorly placed than in *Trichomonas* and showing portions of the cytostome with its stained

border. The axostyle and chromatic basal rod are often the only flagellar structures discernible in *Trichomonas*. The following table shows the association of *Trichomonas* with other protozoa:

TABLE 6.—INCIDENCE OF *TRICHOMONAS HOMINIS*.

	No. cases.	No. specimens.
<i>Trichomonas hominis</i> alone	1	1
<i>T. hominis</i> and <i>Blastocystis</i>	1	1
<i>T. hominis</i> , <i>E. coli</i> and <i>Blastocystis</i>	1	6
<i>T. hominis</i> , <i>E. nana</i> and <i>Blastocystis</i>	1	2
	—	—
Total occurrence of <i>T. hominis</i>	4	10
Incidence of infection: 1.1 %.		

TABLE 7.—INCIDENCE OF *CHILOMASTIX MESNILI*.

	No. cases.	No. specimens.
<i>Chilomastix mesnili</i> alone	2	2
<i>C. mesnili</i> and <i>Blastocystis</i>	1	4
<i>C. mesnili</i> and <i>E. tenuis</i>	1	1
<i>C. mesnili</i> , <i>E. coli</i> and <i>Blastocystis</i>	1	1
	—	—
Total occurrence of <i>C. mesnili</i>	5	8
Incidence of infection: 1.4 %.		

Blastocystis hominis, an ubiquitous organism, is of importance because of the fact that its pleomorphism permits it to mimic ameba cysts. Its actual systematic position has not been established, but it is perhaps more closely related to the fungi than to the protozoa. A full recognition of its range of variation is essential to the accurate diagnosis of intestinal protozoa. In fixed smears stained by the iron hematoxylin method it is seen as a spherical body ranging in size from that of the smallest to the largest ameba cysts. The essential feature upon which recognition depends is the double contoured or crescentic periphery when viewed in optical section. Between these two external membranes will be found small poorly defined masses of stained material. Most of the sphere consists of a large vacuole the contents of which may be the most striking element seen and which may vary in many ways. The contents of the vacuole may be mere hyalin material, may be clear or faintly reticular, or may be reticular and contain irregular masses of stained material deceptively resembling poorly stained nuclei of ameba cysts. In other instances the chromatic material may be more elongated or rod-like and resemble the chromatoidal bodies of ameba cysts. On other occasions the central mass will be dark and cloudy, perhaps containing granules of chromatin, and resembles an overstained ameba cyst. We suspect that technique or chemical factors in the stool affect the morphology of these bodies because there is a tendency for predominance of one or another of these types in any given preparation, and varying from time to time in the same patient. Although *Blastocystis* will scarcely confuse the expert, it is often most confusing to the novice. In unstained

material or after vital staining with eosin, *Blastocystis* has no striking resemblance to the parasitic protozoa, which is an advantage for this method.

The association of *Blastocystis* with other organisms may be seen by revision of the preceding tabulations. In addition, it occurred alone in 79 specimens from 64 patients. It was associated with other organisms in 147 specimens from 63 patients. The incidence of infection in this series is 34.5%.

Summary and Discussion. In a survey to determine the incidence of infestation with intestinal protozoa in patients entering the medical wards of a general hospital in Philadelphia during the winter of 1932-1933, the following results were obtained from a study of 535 fecal specimens from 368 patients:

TABLE 8.

	No. patients.	No. specimens.	Percentage incidence in total group.
<i>Endamoeba histolytica</i> . . .	4	23	1.1
<i>Endamoeba</i> sp.?(probably motile <i>moribund E. histolytica</i>) . .	3	3	0.8
<i>Endamoeba coli</i>	18	33	4.9
<i>Endolimax nana</i>	64	131	17.4
<i>Endamoeba tenuis</i>	26	47	7.0
<i>Iodamoeba bütschlii</i>	4	8	1.1
<i>Dientamoeba fragilis</i>	1	2	0.3
<i>Giardia intestinalis</i>	9	28	2.4
<i>Chilomastix mesnili</i>	5	8	1.4
<i>Trichomonas hominis</i>	4	10	1.1
<i>Blastocystis hominis</i>	127	226	34.5
Negative for protozoa	197	308	53.8

Conclusions. These findings emphasize the importance of amebic infestation in Philadelphia and other cities in temperate climates. There are continually present an adequate number of infested individuals to serve as points of dissemination for future epidemics of amebic dysentery and chronic amebiasis. The practice of sanitation must take this fact into account and so control water supplies and food handling as to assure the destruction of the resistant amebic cysts along with the much more easily killed pathogenic bacteria. The recent epidemic in Chicago might be duplicated in Philadelphia if equal opportunities for dissemination should develop.

The diagnosis of amebic infestation is sufficiently difficult to lead us to emphasize further the fact that special experience, skill and facilities are essential to accurate reports from laboratories of clinical pathology.

Other amebæ, as well as motile mononuclear phagocytic body cells of large size, and *Blastocystis* are frequently confused with *E. histolytica*.

The clinical differentiation of amebiasis from chronic ulcerative colitis, malignancy of the colon, or neurogenic diarrheas, is not always possible.

Only careful, intelligent microscopic search of an adequate number of fecal specimens, properly collected, properly preserved and transported, and preferably aided by proctoscopy, can establish the diagnosis of acute chronic amebiasis.

The authors wish to express their gratitude to Dr. T. Grier Miller for the support and encouragement which made this study possible, and to Dr. Herbert Fox for revision of the manuscript and helpful suggestions.

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THE AGE-INCIDENCE RELATIONS IN DIABETES MELLITUS.

BY GREGORY PINCUS, Sc.D.,

ASSISTANT PROFESSOR OF GENERAL PHYSIOLOGY, HARVARD UNIVERSITY,

ELLIOTT P. JOSLIN, M.D.,

CLINICAL PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; MEDICAL DIRECTOR OF
THE GEORGE F. BAKER CLINIC, NEW ENGLAND DEACONESS HOSPITAL,

AND

PRISCILLA WHITE, M.D.,

PHYSICIAN, NEW ENGLAND DEACONESS HOSPITAL, BOSTON, MASSACHUSETTS.

(From the Laboratory of General Physiology, Harvard University, and the George F. Baker Clinic at the New England Deaconess Hospital.)

A TABULATION of the proportion of diabetics developing diabetes at various ages gives, of course, only the susceptibilities to diabetes of those who have lived long enough to be attacked by the disease. A true picture of the susceptibility to diabetes at various ages is given by the ratio of the number of persons developing the disease to the number exposed to it at these ages. Thus the rate of mortality from diabetes represents the susceptibility of persons to death from diabetes. There are numerous tabulations and discussions of diabetes death rates, but we know of no presentation of the rates of onset of diabetes. We propose, therefore, to present here certain calculations of the onset rates of diabetes mellitus, and to indicate briefly our conception of their significance.

Table 1 contains a summary of diabetes onset data collected between the years 1898 and 1933, and is based upon 9853 cases of true diabetes mellitus. In Table 2 we have made a similar tabulation of the mortalities recorded as due to diabetes in the state of Massachusetts for the years 1901 to 1932.* Derived onset rates (Table 3) are based upon the 1920 life tables for the U. S. registration area. The employment of any other pertinent life table gives substantially the same general result. For purposes of comparison we have also presented in Table 3 mortality rates calculated in exactly the same way as the onset rates were calculated.

TABLE 1.—THE AGE OF ONSET OF DIABETES MELLITUS (EXPERIENCE OF E. P. JOSLIN, 1898-1933).

Decade.	Total number of cases per decade.		Per cent appearing in each decade.	
	Males.	Females.	Males.	Females.
1 . .	230	232	4.96	4.45
2 . .	336	332	7.24	6.37
3 . .	444	317	9.57	6.08
4 . .	638	565	13.75	10.84
5 . .	1082	1197	23.32	22.96
6 . .	1122	1577	24.19	30.25
7 . .	633	822	13.65	15.76
8 . .	150	164	3.23	3.14
9 . .	4	8	0.09	0.15
Totals	4639	5214	100.00	100.00

TABLE 2.—DIABETES AS A CAUSE OF DEATH (MASSACHUSETTS 1901-1932).

Decade.	Total number of deaths per decade.		Per cent appearing in each decade.	
	Males.	Females.	Males.	Females.
1 . .	238	259	2.72	1.93
2 . .	409	397	4.68	2.94
3 . .	414	436	4.73	3.23
4 . .	543	539	6.21	3.99
5 . .	849	1076	9.71	7.97
6 . .	1746	2931	19.97	21.72
7 . .	2515	4420	28.76	32.75
8 . .	1618	2740	18.50	20.33
9 . .	412	694	4.72	5.14
Totals	8744	13496	100.00	100.00

The *method of calculating* may be briefly indicated here. The data for each decade of Columns 4 and 5 of Table 1 are taken as expressing the number of diabetics appearing in each decade out of 100 diabetics identified. Among the males, for example, out of 100 diabetics identified 4.96 are aged 0 to 9.9 years, 7.24 are 10 to 19.9 years old, etc. We can determine by graphic interpolation the number of diabetics for each year of life. Since what we want to know is the ratio of the number of diabetics observed to the number of persons "exposed" to the disease, we turn to the 1920 life tables which give the number of white persons alive in each year of life out of an original quota of 100,000 born alive. Thus, among males, this table tells us that out of 100,000 males born alive 91,567 survive to the end of the 1st year of life. Our incidence statistics state that by the end of the 1st year of life 0.43 male diabetics per 100 or 430 per 100,000 have had

* We are indebted to the Massachusetts Department of Public Health for the data employed.

diabetes onset. The ratio 430/91,567 gives us the onset rate for the first year of life among males. We have followed this procedure for each year of life up to age 90 assuming that diabetes onset does not occur after age 90. Columns 2 and 3 of Table 3 give *relative* onset rates. These are obtained by summing the rates for each year of life and setting the total equal to 100%, and then determining the proportion of this 100% in each decade. For purposes of comparison exactly the same procedure has been followed with the mortality data. We must stress the fact that these calculations are of necessity approximations both because of the method of calculation employed and because of the fact that the incidence data were collected over a period of years when changes in the average length of life and accuracy of diagnosis undoubtedly affected the age-incidence relations. This should be particularly obvious in the mortality data in which we lump data from the Naunyn, Allen and Banting eras. We believe, nonetheless, that our calculations do present sufficiently for our purpose the particular aspects of incidence relations stressed in the succeeding paragraphs.

TABLE 3.—RELATIVE ONSET AND MORTALITY RATES FOR DIABETES MELLITUS DERIVED FROM UNITED STATES LIFE TABLES FOR 1920.

Decade.	Relative onset rates.		Relative mortality rates.	
	Males.	Females.	Males.	Females.
1 . .	3.59	3.22	1.16	0.88
2 . .	5.41	4.74	2.06	1.37
3 . .	7.48	4.73	2.17	1.57
4 . .	11.48	9.06	3.05	2.08
5 . .	21.24	20.69	5.20	4.51
6 . .	24.86	30.48	12.22	13.93
7 . .	18.18	19.90	23.15	26.49
8 . .	7.12	6.23	25.42	26.26
9 . .	0.64	0.95	25.57	22.91
Totals	100.00	100.00	100.00	100.00

In Fig. 1 we have plotted the relative onset and mortality rates for males and females respectively. The onset rates represent the susceptibility to the *development* of diabetes in certain decades, the mortality rates represent the susceptibility to *dying* from diabetes in these decades.

Considering the onset rates alone the figures demonstrate that for both males and females the maximum susceptibility to the development of diabetes occurs in the 6th decade, and our more detailed figures show that age 51 among males and age 55 among females are the ages of maximum susceptibility. The susceptibility of males to the development of diabetes rises steadily to this maximum and thereafter declines. Females, however, have approximately equal chances of developing diabetes in the 2d and 3d decades. Furthermore, their chances of developing the disease are uniformly less than the chances of males until the 6th decade is reached, when their chances then and thereafter are greater than those for males.

To our minds the most significant aspect of these onset rates is the declining susceptibility in the later decades. This indicates

that diabetes is not an old-age disease.* It cannot be taken as a manifestation of senility. Its onset depends upon a complex of events (presumably endocrinal) which attain their maximum manifestation between the ages of 40 and 60. If we take the mortality rates of diabetes as the basis of an incidence study this situation would not be at all clear, for the mortality rates rise steadily until

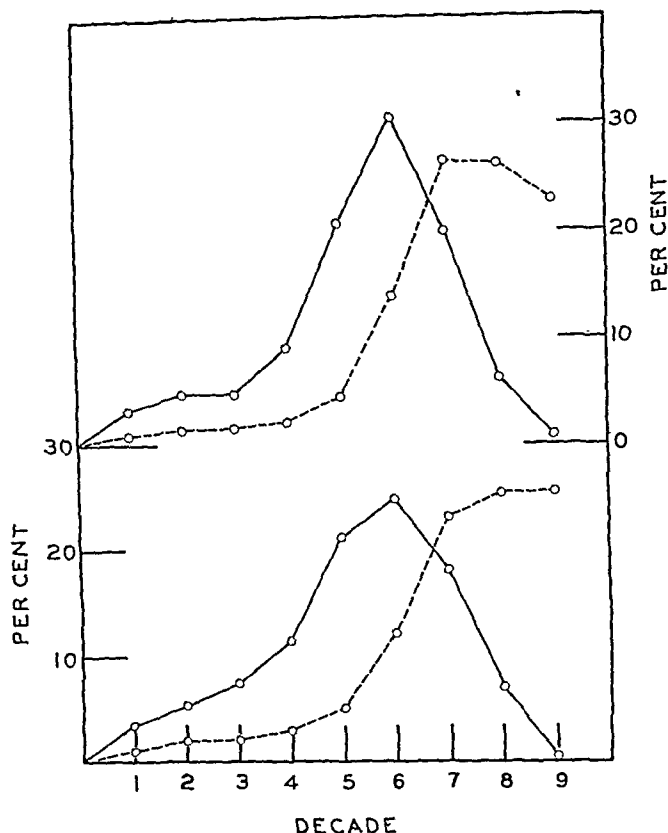


FIG. 1.—Relative onset and mortality rates of diabetes mellitus in the various decades of life. Full lines: onset rates; dashed lines: mortality rates. The upper curves represent the data for females, the lower curves those for males. Abscissa: the decades of life; ordinates: relative mortality in *per cent*.

the 9th decade (*cf.* Fig. 1), and even in this decade the slight decrease (noticeable only in females) is scarcely significant. The mortality rates imply that the older one grows the greater are the chances of dying from diabetes (*cf.* Mosenthal¹), whereas the onset rates indicate that certainly after age 60 is reached the chances of developing diabetes decrease.

* It is interesting to note (1) that diabetics developing the disease after age 60 usually exhibit a mild diabetes, and (2) that the exact time of onset of diabetes in older patients is not as easily ascertainable as in younger diabetics, because the symptoms are less marked and develop insidiously.

The basis of this divergent set of expectations lies, of course, primarily in the length of time diabetes persists before it causes death. If we assume an average duration of the disease of some 10 to 12 years (and somewhat longer in females than in males) these onset and mortality statistics may be taken to corroborate each other. A comparison of the onset and mortality statistics indicates, furthermore, that the duration of the disease before it terminates in death will vary, depending upon the particular age at which it is developed. We feel that these data, however, do not justify any detailed investigation of this relation between age of onset and

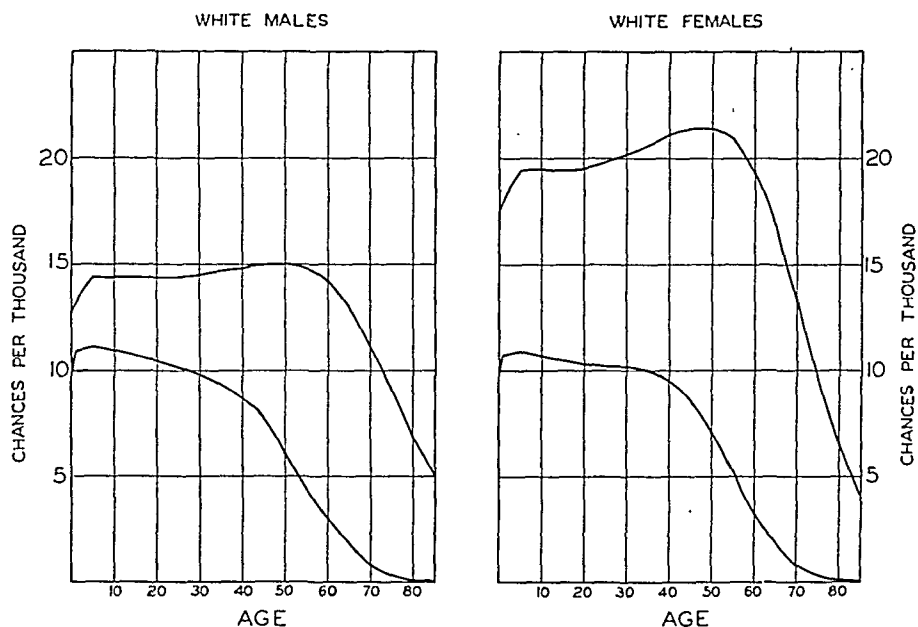


FIG. 2.—The chances of eventually dying from diabetes (upper curves) and of eventual diabetes onset (lower curves). Chances of death are absolute for the death registration states of 1920, and are calculated by the Metropolitan Life Insurance Company. The chances of diabetes onset are relative, *i. e.*, the chances at birth are arbitrarily taken as 10 per 1000 (see text), and are based on the 1920 life tables for the death registration states.

diabetes duration. In fact, the purpose of this communication is to draw attention only to the considerations immediately obvious when onset and mortality rates are compared. The finding, for example, that rising diabetes incidence with age occurs among fat diabetics in contrast to a constant incidence in thin persons (*cf.* Joslin²), would cause an alteration in the shapes of the incidence curves (Fig. 1), although the proportion of thin diabetics would have to be relatively large to alter the general result presented here.

The mortality and onset rates are age-specific and relate the susceptibilities at a given age. Calculations have been made of the chances of *eventually* dying of diabetes³ (Fig. 2). We have made

similar calculations of the chances of eventually developing diabetes on the basis of our onset data. Since we have no absolute statistics of the number of persons developing diabetes we have arbitrarily set the chances at birth as 10 per 1000 and those obtained for all succeeding ages are relative to that arbitrary initial assumption. Since what we are interested in are the relative chances of *eventual* diabetes onset and *eventual* mortality from diabetes this procedure is entirely justifiable. Our comparison then deals with the slopes of the lines of Fig. 2, not with their absolute values. It will be seen at once that the mortality data indicate that the chances of eventual death from diabetes rise to a maximum at age 50 for both males and females, whereas the maximum chances of eventual onset are had at age 5. Furthermore, the chances of eventual death from diabetes begin to decline rapidly at about age 60 and a similar rapid decline in onset chances sets in at about age 40.

We wish to acknowledge the material assistance received from a fund created by Mr. and Mrs. Francis P. Garvan.

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THE PRESENT STATUS OF THE DIAGNOSTIC INTRADERMAL TEST FOR HUMAN TRICHINIASIS.

BY RICHARD D. FRIEDLANDER, M.D.,

ASSISTANT RESIDENT PHYSICIAN, PETER BENT BRIGHAM HOSPITAL,
BOSTON, MASS.

RECENTLY Kilduffe¹ reported the results of intradermal tests performed on 33 individuals recovered from trichiniasis following an outbreak of this disease in Atlantic City, N. J. He came to the conclusions that the demonstration of eosinophilia in human trichiniasis was not only technically simpler than the demonstration of the skin test, but also always feasible; whereas the skin test, requiring an antigen difficult to prepare, was feasible only when the antigen was available; and that the intradermal test in the study of human trichiniasis presents no practical advantages over the demonstration of eosinophilia.

It would appear that some recent publications on the use of serologic methods in diagnosing trichiniasis had not come to Kilduffe's attention, since, if these had been consulted, they would have given a different interpretation to his results. It is the purpose of the present communication to minimize any element of

confusion which might have been introduced by the paper under discussion, and also to review briefly the present status of the diagnostic intradermal test for trichiniasis.

In 1932 Augustine and Theiler² reported a critical study of the value of skin and precipitin tests as aids to diagnosis in this disease in which the skin reactions both in man and swine were described in detail and illustrated in color. The intradermal reaction in these hosts was found to be of the immediate type and was observed to occur within 5 to 15 min. after the injection of the antigen, fading of the reactions commencing during the first hour after the injection. On the other hand, the reaction in laboratory animals, guinea-pigs and rabbits, as described in the early work of Bachman,³ was of the delayed type, being observed usually 24 hrs. after the injection of the extract. The course of the reaction in laboratory animals was found to bear no resemblance to that in man. Moreover these authors noted in their work that many persons were naturally hypersensitive to the antigen in concentrated dilutions, so that in order to rule out non-specific protein sensitivity they employed a 1 to 10,000 dilution of the antigen for routine use.

In 1933 McCoy, Miller and Friedlander⁴ reported a study in which the results of skin tests performed on 88 individuals known to have had trichiniasis were tabulated. The antigen used in this work had been previously subjected to 539 control skin tests and in addition control tests were performed on 232 patients in Rochester, N. Y., 47 in San Francisco and 124 persons in southern Louisiana. The outstanding conclusions of this work were that about 90% of persons ill with trichiniasis will give a positive skin test to the trichinella antigen, provided the disease is sufficiently established. This period was found to be between 2 and 3 weeks after infection in the majority of instances. It was found, in addition, that positive reactions obtained with antigen dilutions of 1 to 10,000 or higher enhanced the specificity of the test and were of more definite diagnostic value than those obtained with lower dilutions. Under the same circumstances it was felt that a negative test would be of relatively greater value in ruling out the disease.*

Presumably not being conversant with this work, Kilduffe used an antigen in a dilution of 1 to 100, did not read his reactions for 24 hrs. after their execution, and employed Bachman's classification of degrees and type of reaction found in laboratory animals as a standard for human infection. His results, therefore, cannot be accepted as revealing the diagnostic value of the test.

Kilduffe is correct that the intradermal test has one disadvantage which does not apply to the demonstration of eosinophilia, providing the latter is present, namely, that the antigen is difficult to prepare

* Further confirmation of these observations have appeared in a more recent paper by Maternovska,⁵ who concludes that the intradermal reaction in man, laboratory animals and swine is specific and diagnostic.

and hence to obtain. Nevertheless this is very different from demonstrating that the intradermal test does not have definite advantages over the demonstration of eosinophilia, when the degree of specificity of the test is considered. Moreover, it is well known that eosinophilia may be present in a large number of other parasitic and allergic conditions and, on the other hand, may be entirely absent in acute fulminating cases of trichiniasis terminating fatally, even when larvæ are demonstrable in the blood and spinal fluid.

Summary. Several years' experience of the author and his former associates, as well as that of Drs. Augustine and Theiler, with the intradermal test in hospitals in San Francisco, Rochester, New York and Boston, where trichiniasis not infrequently occurs, justify the conclusion that it is a valuable aid in the diagnosis of this disease.

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Errata.

We have been informed by the authors that in the March issue of the *American Journal of the Medical Sciences*, on page 378, Paragraph 2, Line 8, the sentence should read, "In over 6 per cent of the syphilitic group, the heart muscle was the seat of infarction."

In Table I. under "Syphilis of aorta," the number of cases of infarct of the heart should be "three" instead of "twelve."

BOOK REVIEWS AND NOTICES.

EXTERNAL DISEASES OF THE EYE. By DONALD T. ATKINSON, M.D., Consulting Ophthalmologist to the Santa Rosa Infirmary and the Nix Hospital, San Antonio, Texas, etc. Pp. 704; 479 illustrations. Philadelphia: Lea & Febiger, 1934. Price, \$7.50.

THIS textbook, dealing with those conditions of the eye which do not require elaborate equipment for diagnosis, covers a portion of ophthalmology in which there are no recent publications in English. The copious illustrations—all new as far as use in a textbook of ophthalmology are concerned—are mostly photographs of drawings or wax models prepared by the author and are almost diagrammatic in the clearness with which the pathologic features are delineated. Included in the appropriate sections are descriptions and illustrations of numerous ocular complications of leprosy.

The text deals with glaucoma, cataract and the ocular muscles, as well as in a strict sense the external eye. Operative treatment and technique occupies a prominent part of each section of the book and the experience and preferences of the author are presented.

The last two sections contain chapters on the hygiene of the eye and prescriptions used in the treatment of ocular conditions.

The volume is one which should be particularly useful to the general practitioner and to the student. The more experienced ophthalmologist, however, would prefer greater detail concerning the anatomy of the eye and pathology of the conditions described. W. F.

DISEASES OF THE SKIN. By OLIVER S. ORMSBY, M.D., Clinical Professor and Chairman of the Department of Dermatology, Rush Medical College of the University of Chicago, etc. With revision of the Histopathology in this edition by CLARK WYLIE FINNERUD, B.S., M.D., Assistant Clinical Professor of Dermatology, Rush Medical College of the University of Chicago, etc. Pp. 1288; 619 illustrations and 3 colored plates. Fourth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$11.50.

"IN order to incorporate new material and yet keep the book reasonable in size much reconstruction has been necessary. Thirty-six new diseases are described, 20 rewritten and the entire work brought up to date. Some of the more important new affections are: Tularemia, thromboangitis obliterans, dermatomyositis and scleredema adultorum. The dermatologic literature has been carefully reviewed in order that this work may reflect its subject as completely as the limits of a single volume permit. As heretofore, articles have been selected on the various subjects which contain complete bibliography to date of publication, thus reducing the number of literature references. These will serve as a guide to the investigative student in working up any particular subject." (From author's Preface.)

EARLY SCIENCE IN OXFORD. By R. T. GUNTHER. Vol. IX. DE CORDE, by RICHARD LOWER, London, 1669. With Introduction and Translation by K. J. FRANKLIN. Pp. 220; illustrated. Oxford: For subscribers at University Press, 1932. Price, £1 1s.

THIS, the ninth of the author's contributions to his study of early science at Oxford, presents a facsimile and good translation of Lower's "epoch

making" (in the author's words) treatise on the heart. While many will perhaps recall the Lower's tubercle of student days, but few realize how important this work was in advancing the new knowledge of the heart and circulation, so gloriously inaugurated by Harvey a generation earlier. Lower's knowledge of the myocardial layers is a case in point. Biographic and bibliographic notices are useful additions, though even more of a background for the translation would have been welcome. E. K.

I REUMATISMI CRONICI. By DOTT. RICCARDO ARRIGONI. Pp. 344; illustrated. Pisa: Casa Editrice W. Giardini, 1933-XI. (Price not given.)

THE vast literature on chronic rheumatism is systematically and concisely reviewed and some original observations added with interpretations of clinical observations in the light of extensive recent experimental advances. All of the well known etiologic factors are discussed in some detail, and the variations in joint manifestations, not only in different individuals but also in the same individual at various periods in his life, are analyzed. The allergic factor is considered one of the most important recent contributions and the author believes that in the future studies of the allergic state will furnish the differential criteria between the various forms of rheumatism. A. C.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY, VOLUME 9, MONOGRAPH 16, PART 1, INFLUENZA. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Honorary Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London, and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 640; 28 plates of illustrations, various charts and tables. Baltimore: The Williams & Wilkins Company, 1933. Price, \$12.50.

PART I of this Monograph on Influenza deals especially with the "Part played by Pfeiffer's Bacillus, Streptococci, Pneumococci, etc., and the Virus Theory." It is, however, a monumental compilation of the literature (both foreign and American) dealing with history, epidemiology, symptomatology (differential diagnosis), mortality and bacteriology of the disease supplemented by personal observations.

The authors are conservative in their conclusions regarding the various bacteria thought at different times to be etiologic agents of the disease, stated, that "although there is much doubt as to whether or not Pfeiffer's bacillus is the primary cause of influenza; there is an almost unanimous agreement that it is the most important secondary invader, even more than the pneumococcus and the streptococcus, and that it is responsible for the great majority of the cases of fatal bronchopneumonia and many other complications. In these cases it occurs in enormous numbers and dominates the picture" (page 516). They feel that whatever the primary cause, "the disease very quickly becomes a symbiotic infection in which the bacteria play a most important and dangerous rôle" (page 568), although the evidence is "insufficient to prove or disprove any etiological relationship between *B. pneumosintes* and epidemic influenza" (page 590). They conclude that the most recent work is "consistent with the view that epidemic influenza in man is caused primarily by virus infection" (page 629), "but cannot accept the evidence, as at present presented, as definite proof that the filterable virus influenza has been cultivated;" (page 628.)

Their own contribution consists of the continued systematic study on a

standardized Crowe's medium of chocolate blood agar with photographic records of the cultures of the bacterial flora of the throat and sputa of the personnel of their research laboratory, at frequent intervals for the past 4 years. These "normal" findings were checked against cultures at the beginning of a catarrhal infection. Their results were reported in 1929, indicating that "normal" flora is 90% streptococcal, varying every week, even in health. They found that a streptococcus caused an epidemic of influenza in 1927 and that one of a different type was occurring in large numbers in the epidemic of 1929. From these findings they "suggest, therefore, that the so-called influenza epidemic may be due to virulent streptococcal infections of the respiratory tract and that these streptococcal infections may vary with the various epidemics" (page 561).

The type is clear, photographic plates are excellent and the entire monograph forms a fitting companion to the previously published volumes.

J. C.

THE CORTICAL LOCALISATION OF CEREBRAL FUNCTION. By PROFESSOR J. SHAW BOLTON, M.D., D.Sc., F.R.C.P., The Henderson Trust Lectures, No. XII. Pp. 23; 23 illustrations. Edinburgh: Oliver and Boyd, 1933. Price, 6d.

THIS lecture is an elaboration of an article published by the author about 30 years ago (Further Advances in Physiology). It gives an excellent summary of the comparative anatomy of the cerebral cortex and of the light thrown upon its function by psychiatry and pathology. It concludes with an interesting review of the important recent paper by Fulton, Jacobsen and Kennard in *Brain*, vol. 55, 1932, on the function of the premotor area.

G. McC.

BACTERIOLOGY FOR MEDICAL STUDENTS AND PRACTITIONERS. By A. D. GARDNER, D.M., F.R.C.S., Fellow of University College; Oxford Member of Research Staff, Medical Research Council. Pp. 276; 31 illustrations, 27 tables. New York: Oxford University Press, 1933. Price, \$2.25.

"THE chief aim of this book is to present shortly, readably, and relevantly as much of the vast subject of bacteriology as a medical student or practitioner needs to know; leaving details of technique to a practical course, and emphasizing the wider biological relations of microbe and man." Adherence to this aim, as set forth in the author's preface, enabled this huge subject to be treated in a small volume. Pathogenic bacteria, fungi and protozoa, as well as filterable viruses, bacteriophage and immunology, have been considered. The material present—of course, only the bare essentials—is up to date. It might be found a little too elementary for present-day medical students, but it should be helpful to practitioners who have been unable to keep up with the recent advances in bacteriology and immunology. It should certainly prove to be highly interesting to laymen.

H. M.

THE GENIUS OF LOUIS PASTEUR. By PIERS COMPTON. Pp. 361, illustrated. New York: The Macmillan Company, 1932. Price, \$4.50.

LIKE his subject, the author of this appreciative "life" has keen regard for the human side of his subject matter. He sees Pasteur as the scientist, to be sure, who "in the interests of his dedication, was forced to live somewhat apart," yet as "one who worked solely for the human element." Admitting that this feature lends warmth to the picture and even can be said to have helped Pasteur toward his great discoveries, it should also be recognized, as the author has apparently failed to do, both that it at times

worked to the detriment of the finished product and also that similar intensities focussed too sharply on one geographical area have marred the contributions to our civilization of other great Frenchmen. The "grandeur of science" must be mingled by Pasteur with "the grandeur of France," on the bright side exemplified by his willingness to give the hydrophobia treatment to Louise Pelletier, a hopeless case (p. 313), on the narrower side by his attitude during the Franco-Prussian war. At the point of death in his paralytic attack (1868), he was heard to murmur, "I am sorry to die, I wanted to do so much more for my country." What he lived to do is known to all, and the appreciation of the French people is shown by the popular vote, easily placing him as the greatest Frenchman of all time. This vivid depiction of an heroic personality should give pleasure to many who perhaps are unfamiliar with Vallery-Radot's fascinating "Life" and with the extensive biographical material that already exists in English. E. K.

MEDICINE IN VIRGINIA IN THE NINETEENTH CENTURY. By WYNDHAM B. BLANTON, M.D. Pp. 466; illustrated. Richmond, Va.: Garrett & Massie, Inc., 1933. Price, \$7.50.

This, the third volume covering the three centuries of Virginia medical history, completes the task undertaken by the author for the sponsors of the work, the Medical Society of Virginia. What it lacks in the picturesqueness of the pioneer and colonial figures it compensates for in the importance of the accomplished work that is portrayed. The story of the rise of 9 medical colleges in a half century, and their later consolidations, typifies current conditions in this country. In the first half century one is surprised to learn the numbers of Virginians who graduated from Northern institutions: in 1819, from the P. & S., 9 from Virginia and 15 from New York; from Pennsylvania, 37 Virginians, 21 Pennsylvanians. In 1841, there were 36 Virginia graduates in a Pennsylvania class of 109; at Jefferson 12 out of 59, and so on. While the ground covered by the 18 chapters of this invaluable reference book is much too extensive for notice here, we note with special interest the chapters on medical societies, journals, the specialties, cults, hospitals and epidemics. E. K.

NEW BOOKS.

Obstetric Medicine. Edited by FRED L. ADAIR, M.A., M.D., F.A.C.S., Mary Campau Ryerson Professor of Obstetrics and Gynecology, etc., and EDWARD J. STIEGLITZ, M.S., M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Rush Medical College of the University of Chicago, etc. Pp. 743; 24 illustrations and 2 colored plates. Philadelphia: Lea & Febiger, 1934. Price, \$8.00.

Lehrbuch der Inneren Medizin, Vols. 1 and 2. By G. v. BERGMANN, and others. Pp.: Vol. 1, 914, Vol. 2, 794; illustrations: Vol. 1, 144, Vol. 2, 146. Berlin: Julius Springer, 1934. Price, Rm. 45 and 49.80.

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PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

PULSE WAVE VELOCITY.

THE increased importance year by year of degenerative cardiovascular disease, portrayed strikingly in our mortality statistics, has renewed with vigor in the past decade the pursuit of studies in arterial function. These studies in a large part hinge upon a study of arterial elasticity, the ability of an artery to stretch a certain amount with a given change in pressure, for arterial elasticity is a measure of arterial efficiency. An index of such efficiency is desirable as a functional test by which the normal and abnormal arterial state may be detected. Measurement of the velocity of the pulse wave has been practically the only method of measurement of this function in significant segments of arteries for the past 50 years.

The evolution of apparatus for the measurement of the velocity of the pulse wave, thought to have reached its height in the discard of ponderable mechanical levers by O. Frank, in the past decade has continued to advance with the introduction of electrical recording units. Bramwell, Hill and McSwiney¹ describe and use the hot-wire sphygmograph. This instrument is based on the principle that a current of air, passing over a hot platinum wire, cools the wire and changes its resistance. Puffs of air from a recording cuff over an artery pass through a tube containing a hot platinum wire, changing its resistance. With the aid of a Wheatstone bridge this change in resistance produces a current which flows through the string of an Einthoven galvanometer, thus graphically recording the pulsation. Because of the relatively enormous surface of the small platinum wire (3600 sq. cm. per cc. of metal) cooling takes place at a rapid rate and very small puffs of air are sufficient to cause a rapid change in resistance. Bramwell² states that lag and inertia are entirely abolished and commencement of upstroke is clearly defined. However, the method is cumbersome, produces a diphasic response, and does not permit the study of wave form.

Turner³ has described a superior recording unit. Carbon grain microphones are placed over the arteries to be studied. As the pulse wave passes under the microphone the resistance in the microphone is changed, varying the current flowing through the instrument. The current passes through a string galvanometer, recording beautiful sphygmographic tracings. This technique possesses all the advantages claimed by the hot-wire method with none of the disadvantages.

Furthermore, the lag entailed in the conduction of air through tubing is entirely eliminated.

More recently Mantoba⁴ has described a recording system consisting of a condensor and an electric amplifier with the 3-electrode vacuum tube. "The movement of the pulse is conducted to the variable condensor, and this tiny movement causes a great change in the direct current of the detector, and this is photographed with the oscillograph." Excellent sphygmograms are obtained and measurement of pulse wave velocity could be done easily by this technique.

The determination of pulse wave velocity as an indication of a diseased arterial state depends necessarily on a knowledge of the normal variation. However, investigations on pulse wave velocity in the healthy individual have not disclosed as yet limits of normal which are generally accepted. The variety of methods used, from the early ponderable lever instruments through the segment capsule of Frank to the newer electrical instruments, have given a wide variation in the figures for normal range. We shall consider here only the results of the more modern technique.

Most workers do agree that pulse wave velocity increases with age. Bramwell, Hill and McSwiney,¹ in 74 subjects from 4 to 84 years of age, obtained pulse wave velocities from 4.7 to 8.6 meters per second, showing a definite relationship between age and velocity, the velocity increasing with the age. The greatest deviation from the mean curve for different ages was less than 1 meter per second. Since pulse wave velocity is a measure of arterial elasticity it can be seen from these data that arterial elasticity diminishes with advancing age.

Moens' original formula⁵ is $V = \sqrt{\frac{E c}{2 p r}}$, in which V is the pulse wave

velocity E the coefficient of elasticity of the artery for lateral expansion, c the thickness of the arterial wall, r the radius of the artery in diastole and p the density of blood. This equation has little practical value because V , c and r are all unknowns and c and r are difficult to determine. Because of this unwieldy formula Bramwell and Hill⁶ derived a formula which by conversion to percentage values finally gave the following relationships:

$$V = \frac{3.57}{\sqrt{\% \text{ increase in volume per mm. of Hg increase in pressure}}}$$

With this formula only one observation (V) is required from which one can calculate the extensibility of the arterial segment studied.

Calculation of the elasticity of the arteries for different age groups by this formula showed that the value is practically halved from 10 to 60 years, adequately explaining the widening of pulse pressure and increase in systolic pressure with age.

Beyerholm⁷ obtained similar results in variation with age, the pulse wave velocity varying from 4.06 to 8.17 meters per second in an age group from 1½ to 78 years. The individual values, however, are slightly higher than those of Bramwell and his co-workers. Hafkesbring and Ashman,¹³ using an optical method, obtained a range from 5.8 to 10.3 meters per second in 90 normal subjects, results which are still somewhat higher than those of Beyerholm.

In all the determinations the diagnosis of a normal individual or one without a certain degree of arteriosclerosis after the sixth decade of life is doubtful.

The relationship of arterial caliber to pulse wave velocity has been a little studied although significant factor. It is only recently that convincing proof of the relationship put forward in Moens' formula 56 years ago has been demonstrated satisfactorily in the intact artery. Bazett and Dreyer⁸ showed that the pulse wave velocity in the brachial and radial arteries was faster and more variable than in the aorta and femoral. Fulton and McSwiney⁹ confirm these findings. The study of the effect of arterial caliber as a single variable upon pulse wave velocity in circulatory schema has not been done satisfactorily. The interrelationship of arterial caliber and arterial tone also remains unsolved.

In contrast to the few investigations on arterial caliber the effect of diastolic blood pressure upon the elasticity of the arterial wall has received much consideration. The thesis that increased blood pressure stretches the artery to a more inelastic state, in this way increasing the pulse wave velocity, has been the explanation of variations in pulse wave velocity with changes in diastolic blood pressure. Bramwell, Downing and Hill¹⁰ have determined the effect of blood pressure on pulse wave velocity in the isolated human artery by the hot-wire technique. Mercury was used as a medium to replace blood because it gives a time interval 3.58 times as long and is much more accurately measurable. By this technique a definite close relationship between blood pressure and pulse wave velocity was demonstrated, although it must be admitted that the results upon an extirpated artery, stripped of its anatomic and physiologic relationships to other tissues in the body, cannot be applied wholly to the intact animal.

Demonstration of a similar relationship between blood pressure and pulse wave velocity in the intact artery in the human has not been uniformly successful. Bazett and Dreyer,⁸ Bramwell, Hill and McSwiney,¹ Hickson and McSwiney¹¹ state that pulse wave velocity in normal individuals varies with diastolic pressure. Sands¹² confirms these results. Others, however, are not in full accord. Fulton and McSwiney⁹ were unable to establish a relationship between arterial blood pressure and pulse wave velocity. The results of Hafkesbring and Ashman¹³ are interesting in that they obtained a significant correlation among women but not among men. Sands,¹² in 14 cases of aortic regurgitation, found no significant change in the range of pulse wave velocity and no correlation with the lowered diastolic blood pressure.

While blood pressure, arterial size, and age have long been considered the important factors affecting the pulse wave velocity in the normal, failure of various observers to confirm results of others suggest that some other factor is operative. In recent years another most important factor has gradually taken its place as an important variable affecting pulse wave velocity. This factor is arterial tone, which affects arterial elasticity presumably through its effect on smooth muscle. I have already referred to the variable pulse wave velocity obtained by Bazett and Dreyer in the peripheral muscular arteries. They suggested the possibility that local conditions of vasoconstriction or dilatation were operative in these determinations. Hemingway,

McSwiney and Allison¹⁴ determined the pulse wave velocity over segments of brachial artery in which they had varied the effective pressure upon the arterial wall by means of a wide armlet under variable pressure. Their calculation of arterial elasticity from these experiments led them to a classification of arteries into hyperextensible, normal and hypoextensible types. This classification of arteries and divergence of their results from the age incidence curve led McSwiney and his associates to believe that smooth muscle tone influenced arterial extensibility. Presumably, they state, this may be influenced by nervous mechanisms through the vasomotor center so that structures with the same histologic appearance may differ widely in their activity. It may be asked, if determinations were made repeatedly at different sittings on these same individuals, whether the same person may at one time fall into the hyperextensible, at another into the hypoextensible or normal groups? This question is not as yet answered.

As long ago as 1917 Dawson¹⁵ presented conclusive proof of changes in arterial elasticity independent of blood pressure. He varied the blood pressure in dogs by nerve stimulation and noted that "the curve of elasticity would, after rising steadily in correspondence with the rise in pressure, suddenly fall or begin to oscillate up and down. Consequently, if one would determine the rate of transmission the pulse wave for a pressure of 60 mm. he might find 10 minutes later that this value corresponded to an entirely different pressure." He concludes that insofar as the pulse wave velocity may be regarded as an index of arterial elasticity it indicates that in the living animal the coefficient of elasticity is irregularly variable, and it is suggested that this variability may be due to changes in the tonus of the vascular walls.

Reuterwall¹⁶ plotted extension curves of extirpated arteries in tests made in rapid succession. Differences were found between successive curves. Treating the same arteries with adrenalin modified the shape of the curves. The arteries used were of the muscular type.

More recently Turner and Sodeman¹⁷ have done repeated determinations of pulse wave velocity in the same individuals to determine spontaneous fluctuations. Their data show that pulse wave velocity may vary widely in the same individual from time to time, the determinations often being in what has been considered the absolutely abnormal range only to return later to the so-called normal range. These results not only change the concept of normal range of pulse wave velocity but demonstrate clearly frequent changes in arterial elasticity which they suggest are changes in smooth muscle tone dependent upon vasomotor responses.

The use of pulse wave velocity as an indication of disease has been applied chiefly to arteriosclerosis, aneurysm and hypertension. The relationship of pulse wave velocity to hypertension is usually explained upon the basis of stretch of the arterial wall to a less elastic state, thus causing an increase in pulse wave velocity. Beyerholm,⁷ from his investigations, concludes that blood pressure and pulse wave velocity are not directly proportionate in their changes. Turner and Herrmann¹⁸ noted that, in some individuals with hypertension, pulse wave velocity actually increased when blood pressure was lowered with nitrites. These results seem to indicate that influences other than simple stretching, as in a rubber tube, are operative in hypertension.

The thickness of the arterial wall was indicated by Moens in his

formula as a factor influencing pulse wave velocity. In the normal individual this factor is of minor importance. Arteriosclerosis, by its increase in the thickness of the arterial wall, as well as by the changes in the wall which reduce its elasticity, with a resultant more rigid tube, would lead to an increase in pulse wave velocity. Bramwell and Hill¹⁹ advocate the use in clinical medicine of pulse wave velocity determinations as direct objective evidence in the diagnosis of arteriosclerosis and aneurysm. In the light of investigations of others, however, their suggestions seem premature. Increase in pulse wave velocity is not a constant finding in arteriosclerosis. Sands¹² says "that from a series of 30 cases of arteriosclerosis in some instances the velocity of the pulse wave is increased and in others decreased." She found in circulatory schema that tortuosity slowed the velocity and believes she can explain the slow velocities on these irregularities of lumen and tortuosity great enough to overcome the lessened expansibility. Measurements of tortuous arteries are also inaccurate, for the tortuosity cannot be measured in the intact individual. Beyerholm,²⁰ in 26 individuals, 25 of whom had arteriosclerosis demonstrable by roentgenography, obtained values averaging 7.52 meters per second, a value a little less than the average for individuals of more than 60 years of age. He does not consider winding of the artery, which he has measured in some instances by dissection postmortem, sufficient to account for the discrepancy between the general conception and his results and states he has not made a deeper investigation of the problem. It can be seen, therefore, that pulse wave velocity as an objective indication of arteriosclerosis is not infallible. The results of Turner and Sodeman, together with the remaining evidence that changes in arterial tone are important in varying arterial elasticity, indicate that pulse wave velocity alone when it is elevated cannot be considered as evidence of organic changes causing increased arterial rigidity, and that temporary or transient variations in arterial tone must be ruled out. Until an adequate method of distinguishing these two factors is forthcoming pulse wave velocity alone, when increased, will be of little use in diagnosis of arteriosclerosis. Furthermore, since demonstrable arteriosclerosis may be present when pulse wave velocity is in normal range, low pulse wave velocity does not eliminate the possibility of arteriosclerosis being present.

Interpretation of low pulse wave velocity in arteriosclerosis has not as yet been attempted by workers in this field further than we have indicated. One must assume that all sclerotic arteries have not lost their elasticity. Arterial tone response to vasomotor stimulation must be investigated. Plesch²¹ has helped open the way to such studies in his consideration of arterial tone. He considers the primary cause of arteriosclerosis a weakening of the muscular and elastic elements of the walls of the bloodvessels. If the weakened bloodvessels are unable to offer sufficient resistance to the blood pressure they become stretched and dilated. Whether or not this is the true situation, Plesch's work has stimulated the study of arterial tone. He sets for arguments to support his views which, although not convincing in themselves, are supported by oscillometric tracings.

W. A. S.

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PEDIATRICS

UNDER THE CHARGE OF
ALVIN E. SIEGEL, M.D.,
MACON, GEORGIA.

CALCIUM METABOLISM AND FACTORS INFLUENCING ITS PHYSIOLOGIC AND PATHOLOGIC VARIATION.

TETANY and spasmophilia have been recognized for years and the relation of parathyroid extirpation to the development of surgical tetany is so well established that preservation of parathyroid tissue in thyroidectomy is an essential responsibility of the surgeon. However, more attention has been attracted to the problem of calcium in the human mechanism during the last decade to the extent that a greater knowledge of its importance in maintaining a physiologic balance has been developed. This development has explained some of the conditions which before were classed from the etiologic standpoint as idiopathic. Among these conditions are tetany and spasmophilia. This subject may be said to be in a state of flux, and an attempt to review the literature may result in a certain amount of confusion; but because the evidence shows that calcium is a most important factor in the normal growth, development and wellbeing, especially in children, this presentation is offered.

Brown and Tisdall¹ state that there are at least 10 inorganic elements which are absolutely essential for life, namely, sodium, potassium, calcium, magnesium, phosphorus, chlorine, sulphur, iodine, iron and copper. "From the standpoint of the practising physician, we are

fortunate in having to watch the supply of only 3 of these elements, because any reasonable diet will furnish the other 7 elements in adequate amounts. The supply of the 3 elements, calcium, iron and iodine, however, should not be left to chance. Although calcium is the fourth most widely distributed element in the earth's crust, its occurrence in foods is quite limited. Our 2 chief sources of calcium are milk and leafy vegetables. As regards the child's diet, it may be stated that it is absolutely impossible to furnish an adequate amount of calcium unless liberal amounts of milk are given. This can be demonstrated readily by the following facts: A diet comparable to that found in many uninformed families composed of rolled oats and bread and butter for breakfast; beef, potatoes, carrots, cabbage and rice for dinner; potatoes, bread and butter, and honey or jam for supper, with 4 ounces of fluid milk to go on the rolled oats and rice—supplies only 0.3 gm. of calcium. Yet the average 10-year-old child requires approximately 1 gm. of calcium each day. The additional 0.7 gm. of calcium required can be furnished by 1 pint of milk per day, or a total milk intake of 24 ounces per day. If all of the milk is omitted, the amount of calcium furnished by the remaining portions of the diet is reduced to the absurdly low figure of 0.17 gm. It is thus evident that we depend mostly on milk to supply the large calcium needs of the growing child."

Daniels, Hutton, *et al.*² studied the relation of the ingestion of milk to calcium metabolism in children. As regards their results they comment in part as follows: "The amount of calcium that a child retains at any given time would seem to be a measure of his physiologic needs at that particular moment, provided enough is available. Single studies cannot determine how much calcium a child of a given age should retain. Balance studies should be made with the same children over a considerable length of time until one can be reasonably sure that they are physiologically full. It seems probable that diets which seemingly have resulted in low retentions have done so, not necessarily because the diets were too low in the given constituent, but because the child being studied needed less and, therefore, took from the amount offered only what he needed. This sometimes has been little, sometimes more. From the results herein reported, it seems clear that 1 pint of milk, when included in a diet which supplies approximately 23% of its calcium from other sources, will supply enough calcium for normal children of the ages studied when a sufficient amount of vitamin D or sunshine is allowed. Whether sufficient calcium will be obtained from diets containing 1 pint of milk when less calcium is given from other sources remains to be determined. Studies of diets which include lower levels of calcium and protein are now in progress." In summarizing their entire work they say: "Retentions of calcium, phosphorus and nitrogen have been determined in children receiving diets differing chiefly in the amounts of calcium, which was furnished by 1 pint and 1 quart of milk respectively. Although wide variation was found to exist in the amounts of these essential constituents retained by different children of approximately the same ages and by the same children under varying conditions of diet and of vitamin D, the results indicate that 1 pint of milk will supply sufficient calcium for the normal child between 3 and 5 years of age, provided the diet furnishes enough protein, phosphorus and vitamins from other sources. The marked

differences in the amounts of the various constituents of growth retained by the same children under varying conditions appear to be due to the physiologic conditions of the children at the time of the study and to their potentialities of growth. Those who had been previously well nourished retained more of the constituents of growth than did those who had been well fed. Normal children between 3 and 5 years were found to retain from 3 to 10 mg. of calcium, from 6 to 8 mg. of phosphorus and from 34 to 90 mg. of nitrogen per kg. It is suggested that the high retentions reported in previous investigations may have been due to the fact that the children under observation were more or less depleted in the substances studied."

Jeans and Stearns,³ in reference to the retention of calcium and the development of bone on diets of evaporated milk, write: "The retention of calcium by the different infants and by the same infants at different periods showed considerable variation, but in general was high. In those periods in which there were definite symptoms of overfeeding (increased frequency of stools), the retention of calcium was decreased. Lowered retentions were observed also after apparent recovery from the infection. During the latter period the infants suffered from the lack of appetite. The serum of each infant was analyzed for calcium and inorganic phosphorus at intervals during the study. The values for calcium ranged between 10.2 and 12.1 mg. per 100 cc. The inorganic phosphorus values were higher than is often reported as normal, varying (with one exception) from 5.2 to 7.3 mg. per 100 cc. These high phosphate values have been observed for several successive years in this clinic in well children given a high intake of calcium and phosphorus, together with cod liver oil. . . . A study of the rate of ossification was undertaken by Miss Idell Pyle, of the Child Welfare Research Station of this university. (University of Iowa.) The average rate of ossification for the group of babies given evaporated milk was definitely above the average for Iowa infants. None of the infants was below the Iowa average; the 2 largest infants were usually within the Iowa average range, sometimes having an increased rate, and the others of the group were well above the Iowa average in the rate of ossification of carpal areas. An increased rate of deposition of minerals in bone and an increased rate of skeletal growth of the infants are indicated by the high mineral retentions, early carpal ossification, rapid growth in length and the entire absence of clinical or chemical evidence of rickets. The same factors offer abundant evidence that the amount of calcium retained from evaporated milk feedings, when these are accompanied by the dietary additions used with these infants, is amply sufficient to provide for excellent growth and development of bone. This finding is perhaps of particular interest in view of the retention of calcium observed in infants on pasteurized milk and is in line with the observations of Willard and Blunt, and of Kramer, Latzke and Shaw. Willard and Blunt found that evaporated milk is slightly superior to pasteurized milk as a source of calcium, phosphorus and nitrogen for children. Kramer, Latzke and Shaw observe that pasteurized milk gives less favorable calcium balance than evaporated or fresh milk"

Stearns⁴ summarizes his results as follows: "The excretion and retention of nitrogen, calcium and phosphorus of an infant fed milk and various soy bean preparations have been determined. The rela-

tive proportions of nitrogen, calcium and phosphorus ingested differed with the diets. An increase in the relative intake of nitrogen and calcium, as compared to the phosphorus intake, resulted in an insufficient retention of phosphorus. Under these conditions the urinary excretion of calcium was tremendously increased, and the urinary phosphorus markedly decreased. The excessive excretion of calcium in urine noted with two of the diets is interpreted as evidence of an absorption of calcium greatly in excess of the amount which can be deposited in bone with the limited quantity of phosphorus available. The marked alteration in urinary secretion of phosphate was without apparent effect on the excretion of sulphate and chlorid in urine. Excessive excretion of calcium in the urine was accompanied by a shift in the mode of excretion of the other bases, decreasing the excretion in urine and increasing the fecal excretion. The altered calcium metabolism does not seem to affect the retention of fixed bases other than calcium. The substitution of dicalcium phosphate for calcium carbonate in the soy bean food improved the relative retentions of nitrogen, calcium and phosphorus. The modified soy bean food, from our observations, appears to be a satisfactory food for infants. It is concluded that in the feeding of infants the relative proportions of nitrogen, calcium and phosphorus in the diet are fully as important as the absolute intake of these elements. From the results of this study, it is suggested that, as the relative proportions of these elements in cows' milk allow adequate retention, this ratio seems a safe guide to follow."

From the foregoing it is seen that there is a definite relationship between calcium and other elements. Later will follow abstracts indicating the rôle played by the endocrine system in influencing this balance with special reference to the parathyroids. A paper entitled "The Effect of Calcium on the Storage of Colloid in the Thyroid Gland" suggests a reversed effect on another component of the endocrine system. Klein⁶ made a series of studies on 36 young white rats. He introduces his presentation as follows: "For some time iodine has been emphasized as the most important factor in thyroid function. Iodine, however, is only one factor. Calcium is another element necessary to proper thyroid function. Various aspects of the problem have been discussed by Berry, Hellwig, Kottman, Abelin and Thompson. As the latter has stated, both calcium and iodine exert important influences on the thyroid, the normal function of which seems to depend on a proper relation between these two elements. Calcium in limestone areas has been stressed as an important factor in the causation of goiter, through a water supply rich in this element. More recently Hellwig has demonstrated that excess of calcium in the presence of iodine deficiency causes hyperplastic changes in the thyroid. The results of his investigations suggest again that normal thyroid function may depend on the conjoint action of calcium and iodine. The purpose of my study is to determine what influence calcium exerts in the storage of colloid in the thyroid, particularly in the presence of thyroglobulin as well as of an excess of iodine in the water supply. The investigation was begun as the result of an interesting clinical experience in which the administration of calcium exerted a definite curative effect in acute hyperthyroidism. This raised the question: What effect has calcium on the function and structure of the thyroid gland which gives it thera-

peutic properties in clinical hyperthyroidism?" He summarizes his results as follows: "Calcium either by mouth or hypodermically increases the amount of colloid in the thyroid gland in the rat in the presence of thyroglobulin and iodine. Intercurrent respiratory infection may cause a decrease of colloid storage and of hyperplasia. Even in these animals calcium increased the storage of colloid. The therapeutic action of calcium in hyperthyroidism may be due to this property of increasing colloid storage in the presence of an excess of thyroglobulin."

On the other side of the picture the parathyroid glands are a part of the mechanism concerned with calcium metabolism. Removal of these results in tetany, a clinical picture associated with low serum calcium concentration. Schelling and Goodman⁶ treated 2 patients suffering from postoperative parathyroid tetany with low phosphorus diets. This procedure was based on the known relationship between serum calcium and serum phosphorus concentration. Studies were made of the effect of calcium, magnesium, parathyroid extract and vitamin D on the concentration of calcium and inorganic phosphorus in the serum and on the excretion of these substances in the urine. They state: "The advantages of the low phosphorus diet in the treatment of parathyropivic tetany are as follows: (1) It prevents phosphorus retention and thereby allows the serum calcium to approach non-tetanic levels. (2) Less calcium is needed to rid the body of the retained phosphorus as the insoluble salt. (3) It minimizes or dispenses with the use of parathyroid extract in cases with marked phosphorus retention and thus reduces the possibility of metastatic calcification and renal impairment. (4) It obviates the use of vitamin D, since its administration in the presence of phosphorus retention may predispose to metastatic calcification. (5) The diet may be derived from a variety of food substances and thus eliminates the monotony of eating the same articles of food daily. (6) The treatment may be continued at home without inconveniencing the patient and without the need of too frequent analyses of the blood for calcium, as when parathyroid extract is used. Menus for low phosphorus diets may be easily calculated from tables given by Sherman and by Simmonds. The added calcium may be given as the lactate or the carbonate and the magnesium as the lactate, to prevent transient or permanent tetany, in renal rickets and in nephritis with phosphorus retention. The use of high calcium diets for the treatment of nephritis with phosphorus retention was previously suggested by Briggs."

Craig⁷ introduces report of a case of tetany of the newborn by saying that the medical literature is rich in statements that tetany does not occur in the newborn. Many instances of convulsions in the newborn undoubtedly are cases of tetany. Perhaps many pediatricians and physicians have erred in the same manner as the Reviewer in failing to publish their cases of convulsions in the newborn responding favorably to the injection of calcium solutions. Craig says: "The striking factors in this case were the absence of marked tetanic symptoms, such as true spasticity and cardopedal spasm and the rapid response to calcium medication. I think that any newborn child having convulsions when the spinal fluid is negative should have the therapeutic test of calcium administration, regardless of the lack of the more classical signs and symptoms of so-called tetany. Certainly no harm can be done. The purpose of reporting this case is to emphasize that

convulsions in the first few days of life may not be due to birth hemorrhage, that the symptom complex, tetany of the newborn, does occur in the early days of life. Whenever there is doubt, the infant should be given the benefit of calcium medication."

Small⁸ reports a case of tetany developing on the 9th day of life. His patient, at the age of 3 years and 9 months, had made normal mental and physical progress with no recurrence of the convulsions. His comment is quoted: "Benita Wolff quoted by Klose bases considerable importance on increase of irritability, and says, 'Chvostek sign is pathognomonic,' and does not accept a diagnosis without evidence of increased galvanic irritation. In the light of the work of Stevenson, Mitchell and Koch, who found in normal newborn infants from 12 hours to 21 days, that a Chvostek sign occurred consistently without serologic or electric evidences of tetany, also in view of the fact that the case herein reported as well as Power's case not showing a Chvostek sign, this sign is made of questionable importance. It certainly removes it from the category of 'pathognomonic signs.' At the present time the consensus of opinion favors the view that a lowered blood calcium is the pathognomonic sign of tetany, especially if other diseases in which a low serum calcium is present are excluded. What causes this lowering of blood calcium obviously is not clearly understood and has been the basis of considerable discussion. That there seems to be a sufficient storage of calcium elsewhere in the body is proved by the fact that a patient with tetany and a lowered blood calcium can be cured without additional calcium being given. Thus the administration of cod liver oil and viosterol as well as ultraviolet irradiation are agents which have been used successfully. Parathormone has also been used to raise the blood calcium to normal levels. Gamble and coworkers showed successful results with the use of acid-producing substances, such as hydrochloric acid, ammonium chlorid or calcium chlorid. There are several interesting facts brought out in this case study. First, that tetany may occur in bizarre form with only a few of the so-called conventional symptoms and signs. Secondly, the condition readily simulated birth injury, although a little late in onset of symptoms. Whether or not a relationship existed between the mother's mild toxemia or antecedent infection (Vincent's) and the baby's symptoms is speculative. It would seem likely that in view of the temperature an infection played some part in precipitating an attack, even though the nature of the infection was not demonstrated."

Wilder, Higgins and Sheard⁹ studied the significance of the hypertrophy and hyperplasia of the parathyroids in rickets and osteomalacia by a series of experiments with chicks. Their conclusions are quoted: "Experiments with chicks reveal that deprivation of vitamin D, sufficient in degree to cause rickets, will produce hypertrophy and hyperplasia of the parathyroid glands; that the parenteral administration of parathormone in such minor degrees of deprivation of vitamin D prevents this hypertrophy and hyperplasia, but that when the deprivation of vitamin D is extreme, so that rickets is clearly in evidence, administering parathormone may restrict but will not prevent the hypertrophy and the hyperplasia of the glands. It appears from this and other evidence cited that the hypertrophy and hyperplasia of the parathyroid glands of chicks, under conditions of deficiency of vita-

min D, depend on their accelerated functional activity. Other observations are interpreted to mean that the supply of parathyroid hormone determines the sensitivity of the organism to the action of vitamin D. A diminished supply of the hormone, as after parathyroidectomy, diminishes the ability of the organism to function normally with restricted amount of vitamin D; an augmented supply conditions the tissues of the organism so that the effects of the vitamin are more intense, and so that amounts of the vitamin, which otherwise would not prevent rickets, do prevent rickets. By virtue of the capacity of the parathyroid glands to accelerate the rate of supply of their product, and owing to the resulting conditioning of the tissue (increased sensitivity to vitamin D), the organism is enabled to withstand periods of relative deficiency of vitamin D which otherwise would produce rickets or osteomalacia. This compensatory mechanism is adequate to protect against relative degrees of deficiency of vitamin D; it is inadequate, as would be expected, when deficiency of vitamin D is extreme." Excessive activity of the parathyroid results in a typical clinical picture.

Bauer¹⁰ says: "Hyperparathyroidism or generalized osteitis fibrosa cystica is a clear-cut, distinct disease entity caused by an increased secretion of the parathyroid hormone. . . . All cases thus far reported have been due to a parathyroid adenoma. The fact that it is a disease of endocrine origin implies that the entire skeleton is affected. Arthritis and Paget's disease are never generalized skeletal diseases. This fact alone argues against their being of parathyroid origin. Hyperparathyroidism is a disease characterized by definite alterations in the calcium and phosphorus metabolism as well as by certain symptoms and signs. The alterations in the calcium and phosphorus metabolism are: (1) An elevated serum calcium. Serum calcium values as high as 23.6 mg. per 100 cc. have been reported. The normal serum calcium varies between 9.5 and 10.5 mg. (2) A decreased serum phosphorus. Values as low as 1.4 mg. per 100 cc. have been observed, in contrast to normal values of 4 to 5 mg. (3) An increased calcium excretion. The increased excretion of calcium is entirely urinary, the fecal excretion being unaffected. (4) An increased phosphorus excretion. The increased excretion of phosphorus is also entirely urinary. The increased excretions of calcium and phosphorus in 1 reported case were of the same magnitude as those in a normal individual receiving 100 units of an active parathyroid extract per day. These alterations in the calcium and phosphorus metabolism may be accompanied by any or all of the following symptoms and signs: (1) Polydipsia; (2) polyuria; (3) weakness and loss of strength; (4) constipation; (5) loss of appetite; (6) loss of weight; (7) indefinite muscle and joint aches and pains, commonly diagnosed rheumatism, arthritis or neuritis; (8) bone tenderness; (9) frequent fractures, often following slight trauma; (10) decreased excitability of the nerves; (11) skeletal shortening; (12) kyphosis; (13) bone tumors, frequently diagnosed epulis of the jaw or giant-cell tumor in other bones; (14) kidney of ureteral stones (usually bilateral); (15) characteristic Roentgen ray findings, such as generalized decalcification, bone tumors, multiple bone cysts, fish type vertebral bodies, etc.; (16) frequently anemia with leukopenia. In view of the above facts no patient should be subjected to a parathyroidectomy until sufficient evidence has been gathered from the history, physical examination, Roentgen examination and metabolism studies to leave no doubt as

to the correctness of the diagnosis of hyperparathyroidism. Until some simple test for hyperparathyroidism is devised, all suspected or questionable cases of hyperparathyroidism should be very carefully studied. Serum calcium and serum phosphorus determinations should be made and, if possible, serum phosphatase as well as total calcium and phosphorus metabolism studies. It certainly behooves us to proceed cautiously before making or accepting any statement which implies that certain cases of arthritis are due to hyperparathyroidism or that Paget's disease is of parathyroid origin. No findings have been seen that would suggest the existence of hyperparathyroidism as a causal factor. True, many of the cases of rheumatoid arthritis show Roentgen ray evidence of decalcification (bone atrophy). However, this is no more than we often see associated with disuse. Furthermore, we know that the calcium excretion of a patient when immobilized in a cast is much higher than when this same patient is allowed ordinary ward activity. The improvement reported in cases following parathyroidectomy may have been due to anesthesia, rest in bed, or a natural remission of the disease. These 3 factors are all capable of bringing about improvement, particularly in cases of rheumatoid arthritis. Because the latter disease is characterized by remissions and relapses, improvement is often ascribed to a particular form of therapy, whereas in reality it may represent nothing more than a natural remission."

During the past 2 or 3 years a number of contributions on the subject of hyperparathyroidism have appeared. A few of these are enumerated: Pemberton,¹¹ Schultzer,¹² Sainton,¹³ Rankin and Priestley,¹⁴ and Cohen and Kelly.¹⁵ Under the title of "Parathyroid Tumors Without Osteitis Fibrosa," Hadfield and Rogers¹⁶ report 2 tumors of the parathyroid gland. One occurred in a woman, aged 58, the other in a man, aged 51. The bulk of the tumors was relatively enormous. In 1 there appeared at first to be some reason for regarding the enlargement as being etiologically related to the skeletal changes of frank acromegaly, associated with a large chromophil adenoma of the pituitary. In the other an adenoma, indistinguishable as far as could be judged by ordinary histologic methods from those described in general osteitis fibrosa, was associated with a radiologically normal skeleton. The authors have been able to find only 6 previously reported cases of parathyroid adenoma or hyperplasia associated with pituitary disease. They do not think that this association is so rare as this figure indicates. They think that the skeletal overgrowth of acromegaly alone should, theoretically, make excessive demands on the parathyroids. After some argument they conclude that in the first of their 2 cases the adenomatous enlargement of the parathyroid was unrelated to the skeletal changes; in other words, they place it in the same category as their second case. They point out that since Mandl restored the calcium metabolism to normal in a case of osteitis fibrosa by excision of a parathyroid tumor, and thus disproved Erdheim's theory according to which the parathyroid adenomata in these cases were secondary to the disease of the skeleton, the publication of similar cases has given rise to the impression that a parathyroid adenoma must of necessity be associated with diffuse skeletal softening. They hold that their 2 cases prove this to be fallacious. In their opinion it seems likely that parathyroid tumor, closely resembling the normal gland, may occur without elaborating any excess of internal secretion.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 21, 1934

An Improved Colorimetric Method for Determining Sulphate in Serum and Urine Adaptable to the Determination of Sulphate Clearance.—T. V. LETONOFF and J. G. REINHOLD (Laboratories of Philadelphia General Hospital). Sodium-beta-naphthoquinone-4-sulphonate (Folin's amino-acid reagent) develops an intense and stable color with benzidin. The chromogenic power of this reaction is far greater than that of the unsatisfactory ferric chlorid-hydrogen peroxid reaction used by Wakefield in his modification of the Hubbard microsulphate method.¹ A procedure for the determination of sulphate in serum and urine has been developed utilizing the reaction of benzidin sulphate with the amino-acid reagent in the presence of a sodium borate-sodium hydroxid buffer. Acetone is added after the color reaction is completed to diminish the color of the reagent. An additional innovation for the determination of sulphate is the use of uranium acetate for the removal of proteins. This reagent removes phosphate as well, consequently error due to precipitation of benzidin by phosphate when increased concentrations of the latter are encountered is avoided. Determinations of sulphate in urine by the modified method agree closely with the results by Folin's gravimetric method. Recoveries of sulphate added to serum tended to be low, but were within limits permitting the use of the method for sulphate clearance determination.

The Prophylaxis of Anaphylaxis in the Actively Sensitized Guinea Pig.—A. H. ZIFFERBLATT and H. K. SEELAUS (Laboratory of Immunology, Philadelphia College of Pharmacy and Science). Guinea pigs actively

¹ Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, The Williams & Wilkins Company, vol. 2, 1932.

sensitized with horse serum were protected from anaphylactic shock by treatment with an iodine solution. This solution was prepared by forcing iodine vapor into sterile distilled water by means of a pump. When completed, the solution contained 0.0079 gm. per cc. of the fluid, hydrogen-ion concentration 4.6, specific gravity 1.037. The treatment of previously sensitized animals consisted of intraperitoneal injections of 0.5 to 0.85 cc. of the solution until 10 or 12 cc. had been administered. Either of these amounts was found sufficient to desensitize the animal. Toxicity due to cumulative effect of the drug, used therapeutically, was not observed. The solution proved toxic in quantities of 2 cc. and 3 cc. in animals weighing 410 and 790 gm. respectively

The writers believe for the present that the iodine is assimilated by the cells chiefly affected in anaphylaxis and causes a change in their chemical constitution. This change induces an altered reaction capacity of the cell toward the specific antigen, thus conferring immunity on the animal to subsequent shock when the antigen is reinjected.

The Syneresis of Blood Clots: The Rôle Played by the Blood Platelets.—L. M. TOCANTINS (Department of Medicine, Jefferson Medical College). The dispute over the rôle, if any, that the platelets play in the syneresis of blood clots can be traced to differences in methods of counting platelets and of estimating syneresis, and to the ambiguous use of this term. A distinction should be drawn between spontaneous syneresis and that following artificial separation of the clot from the walls of the vessel. By a series of experiments consisting in the addition of antiplatelet serum and of intact and destroyed platelets from different animals, in various amounts, at different locations, to normal or deplateletized blood or recalcified oxalated plasma, the following conclusions were arrived at: (1) Spontaneous syneresis of blood clots is almost wholly a function of the blood platelet; (2) only the intact, undestroyed platelets can bring about spontaneous syneresis; (3) that property of the blood platelets is not species specific.

The Origin of the VIIth and VIIIth Cranial Ganglia in the Amphibian Embryo.—C. L. YNTEMA (Laboratory of Anatomy, University of Pennsylvania). The origin of the VIIth and VIIIth cranial ganglia was studied in the embryo of *Amblystoma punctatum*. The method used was to transplant ectoderm from an embryo which had been stained with Nile-blue sulphate to the orthotopic position on an unstained embryo. The stain in the granules was preserved in sections.

It was found that the different sources of the ganglia were separable. The neural crest made a small contribution which was situated in the roots of the VIIth and VIIIth nerves. The remaining and greater part of the VIIth ganglion was derived from the pre-auditory placode and the hyomandibular epibranchial placode: the former contributed the anterolateral and ventrolateral ganglia; the latter, the facial ganglion. Aside from the small neural crest contribution, the VIIIth ganglion was derived from the otic vesicle.

The Conduction of Cortical Impulses to the Autonomic System.—E. A. SPIEGEL and W. C. HUNSICKER, JR. (Department of Experi-

mental Neurology, D. J. McCarthy Foundation, Temple University School of Medicine). The conduction of cortical impulses to vegetative organs was studied in 30 cats.

In the first series of experiments "extrapyramidal" fibers arising from the hypothalamus were severed. In a second series of experiments a transverse section of both pyramidal tracts was made. After the lesion on either of these systems had been performed, the effects of stimulation of the motor cortex and the frontal lobe was noted on the pupil, the bloodvessels, the sweat glands and the urinary bladder.

In both groups of experiments the cortical stimulation elicited reactions of the above-mentioned organs. It is, therefore, concluded that there exists a double (pyramidal and extrapyramidal) conduction of corticofugal impulses to the autonomic centers in the cord.

Vasomotor Reflexes in the Splanchnic Area.—G. D. GAMMON¹ and D. W. BRONK (Eldridge Reeves Johnson Foundation for Medical Physics, University of Pennsylvania). Sensory zones concerned in the reflex control of blood pressure have been found in endings of nerves surrounding the vessels of the splanchnic areas. The most important factor conditioning the discharge of impulses appears to be the state of distention—hence the volume of blood—of the splanchnic vessels. The endings responsible are Pacinian corpuscles in the mesentery. Preliminary experiments tend to indicate that the nervous discharge set up by distension of the vessels effects a reflex contraction of the vessels in this region. Because of the significance of the splanchnic area in control of blood pressure the importance of this afferent mechanism is stressed.

¹ Godey Fellow in Medicine.

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AUGUST, 1934

ORIGINAL ARTICLES.

THE STORY OF THE DEVELOPMENT OF OUR IDEAS OF
CHEMICAL MEDIATION OF NERVE IMPULSES.*

By WALTER B. CANNON,

GEORGE HIGGINSON PROFESSOR OF PHYSIOLOGY, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

THE story of the growth of our knowledge that nerve impulses affect smooth muscle, cardiac muscle and some digestive glands by setting free a chemical mediator I have chosen for a variety of reasons. First, it is a relatively new story, descriptive of recent advances of knowledge, that promise important fresh insight into still unknown realms of physiology and medicine. Again, it illustrates to an unusually striking degree the ways in which science may progress, with the early bold projection of novel ideas, the hesitant and tentative groping of investigators in unfamiliar territory, the performance and reporting of experiments the full significance of which was not at the time well understood, the occurrence of flashes of perspicacity, the slow accumulation of facts that lead to conviction, the illumination of old, dark mysteries in the light of the new truth, and the forward look toward further exploration in the twilight zone of ignorance that surrounds us. In the brief time available I shall not be able to tell the story in full detail; instead, I shall lay emphasis only on its salient features.

The meaning of chemical mediation of nerve impulses is made clear by reference to the first intimation of its existence. In 1904 T. R. Elliott,¹ then a young student of physiology at Cambridge, England, was struck by the fact that long after sympathetic nerves had been cut and degenerated, the structures previously innervated

* The Kober Lecture, delivered at Georgetown University, March 28, 1934.
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by these nerves (smooth muscle, for example) respond in a characteristic manner to adrenin—contracting in response to this agent where sympathetic impulses formerly caused contraction, and relaxing where they formerly caused relaxation. Obviously the adrenin did not affect any structure dependent on the peripheral nerves, for they had degenerated. Elliott thereupon offered the highly important suggestion that whenever a sympathetic nerve impulse arrives at a smooth-muscle cell, it may liberate adrenin locally in the cell, and that this adrenin acts as a chemical step in the process of stimulation. In Elliott's own words, adrenin "might then be the chemical stimulant liberated on each occasion when the impulse arrives at the periphery." The fact that adrenin from the adrenal glands mimics the action of sympathetic impulses would thus be explained; it is the same substance as that which, in Elliott's idea, serves locally as an intermediary between the impulses and the special reacting mechanism in the cell.

As already noted, in some smooth-muscle cells sympathetic impulses, and also injections of adrenin, cause contraction and in others relaxation. The impulses can be artificially produced by electric shocks, and thus they can be made the same in duration and frequency for the two opposite effects; and the adrenin likewise is the same for both. How, then, may these quite contrary effects of the same agents be explained? In 1905 Langley,² the Cambridge physiologist, puzzled by the facts, published the hypothesis that in reacting cells two sorts of "receptive substances" exist, excitatory and inhibitory. When adrenin reaches a cell, he surmised, its action is determined by the kind of receptive substance there present; if it unites with the excitatory substance contraction results, and if with the inhibitory, relaxation. As we shall see, many years later Langley's idea received experimental support.

Another step in the development of the concept of chemical mediation of nerve impulses was taken in a research published in 1906 by Howell³ of Baltimore. The resemblance between the inhibition of the heart induced by potassium salts and that induced by vagal stimulation had led Bottazzi,⁴ in 1896, to suggest that the two are identical in character. Martin⁵ had brought forward further evidence for that conclusion in 1904. Working on the idea that the vagus might exert its inhibitory influence through the agency of potassium compounds, Howell found that the efficacy of vagal impulses varied with the amount of potassium salt in the perfusing fluid, and he drew the inference that the impulses act indirectly by increasing the amount of diffusible potassium compounds in the heart tissue. That was in 1906. Two years later Howell and Duke⁶ reported that vagal stimulation causes an increase of the potassium content of Locke's solution perfused through an isolated mammalian heart, and they regarded the results as favoring the view that vagus nerves exercise their cardio-inhibitory

influence through the direct action of diffusible potassium compounds which vagal impulses set free. Although the concept of chemical mediation is here clearly expressed, and experiments justifying that concept are reported, neither the theory of potassium inhibition nor the data in support of it have fitted into the progressive developments which have led to our present understanding. We now know that an inhibitory chemical substance is, indeed, readily liberated in cardiac tissue by vagal impulses, and that like those impulses, but unlike potassium salts, it is blocked by atropin. I must not, however, anticipate events!

The next suggestion which finds its place in this historical sequence was published by Dixon and Hamill,⁷ in 1909. They drew attention to the resemblance between the effects of nerve stimulation and the effects of certain drugs. "There is no inherent difference," they wrote, "between the action of muscarine on the heart on the one hand, and electrical excitation of the vagus nerve on the other. So similar are the two effects that it is not unwarrantable, in the absence of any evidence to the contrary, to assume that they are brought about in the same way. If it is permissible to argue from analogy, there is reason in the suggestion that excitation of a nerve induces the local liberation of a hormone which causes specific activity by combination with some constituent of the end organ, muscle or gland." Note that this idea is essentially the same as that expressed earlier by Elliott, the only difference being that muscarin is proposed as the intermediary for vagal impulses, whereas Elliott had suggested adrenin as the chemical agent for sympathetic impulses. These guesses by Dixon were not put forth without efforts to secure an experimental basis for them. It appears that he had killed animals by pithing them, had let them bleed, and then had stimulated the vagus nerves for half an hour. An extract of the heart, made thereafter, "was found to have the power of inhibiting the frog's heart, and like muscarine the effect was completely antagonized by atropine." This highly suggestive observation Dixon⁸ published in an obscure journal, *The Medical Magazine*, in 1907. I learned of it by reading the obituary notice of Dixon published by Gunn,⁹ in 1932. Gunn testifies that he once asked Dixon why he dropped this research in which he had made such interesting beginnings and received the reply that he was deterred by the universal skepticism with which his views were received!

It is probable that reports by Dale¹⁰ and by Dale and Ewins¹¹, in 1914, played a rôle in the further development of our knowledge of chemical transmission of nerve impulses. Before their work is detailed, however, mention should be made of a discovery reported about 8 years before by Hunt and Taveau.¹² Noting that in aqueous extracts of the adrenal gland a blood-pressure reducing substance was present which, on chemical treatment, disappeared

as the cholin content increased, Hunt had inferred as early as 1901 that in the extract there might be an esterlike precursor of cholin. With Taveau's coöperation a number of esters were made, among them acetylcholin which proved to be a most remarkable substance, being a hundred thousand times more active than cholin in causing a fall of blood pressure, and a hundred times more active in that effect than is adrenalin in causing a rise. In the reports by Dale in 1914 the fact was brought out that certain ergot extracts produced changes in the body closely resembling those produced by muscarin, and that the agent responsible for them was acetylcholin, *i. e.*, the muscarin action might be due to the presence of a cholin ester in its chemical structure. The effects observed when acetylcholin was injected included, Dale stated, a "pronounced vagus-like inhibition of the heart, and various other effects of stimulating nerves of the cranial and sacral divisions of the autonomic system—secretion of saliva, contraction of the œsophagus, stomach and intestine, and of the urinary bladder." These effects, which were very brief, were abolished by small doses of atropin. Here we have definitely the intimation that acetylcholin mimics the action of parasympathetic nerve impulses, much as adrenin mimics the action of sympathetic impulses. It seems probable that this hint would have been promptly seized and worked upon if the World War had not forced the attention of investigators to more urgent matters.

It is noteworthy that up to this time there was no satisfactory experimental evidence supporting the hypotheses which had been offered. Indeed, 7 years passed before any further progress was made, and then, in 1921, two researches were published, one a contribution the significance of which was not appreciated at the time, and the other a recognized forward move in the developing course of events. The former research was conducted by Uridil and myself; the latter by Otto Loewi, the Austrian pharmacologist.

Uridil and I¹³ were concerned primarily with a criticism which had been brought by Stewart and Rogoff¹⁴ against my use of the denervated heart as an indicator of the secretion of adrenin. I¹⁵ had reported that a stimulus applied to the splanchnic nerves caused the denervated heart to beat faster if the adrenal glands were intact, but that after removal of the glands the same stimulus had a minor effect. Stewart and Rogoff, on the other hand, noted that, with the glands removed, direct splanchnic stimulation still caused a considerably faster rate of the denervated heart—a result which, they declared, they were not called upon to explain, but which they attributed chiefly to the attendant rise of arterial pressure. Since it was well known that variations of arterial pressure would not alter the rate of a well-nourished isolated heart, their suggestion was lacking factual support. We were convinced that there was "some other hitherto unknown factor at work

causing the faster rate," and we started out to find it. Our experiments led to evidence that splanchnic stimulation, after the adrenals are extirpated, causes the discharge of a substance from the liver, a substance which, like adrenin, accelerates the heart and raises blood pressure, and that these effects are slight if the animals have been fasting but considerable if they have been digesting meat. Thus was explained the discrepancy between the earlier results which I had obtained—for I had used fasting animals—and the results of Stewart and Rogoff, who had not paid attention to the digestive state. The centering of interest on conditions which affect secretion from the adrenal medulla unfortunately led to a prolonged neglect of our suggestive observations. Not until years later did it become clear that the cardio-accelerator substance from the liver has properties linking it with Elliott's suggestion of an adrenin-like mediator of sympathetic nerve impulses.

In conversation Loewi has given an interesting account of the origin of his experiments. One night, having fallen asleep while reading a light novel, he awoke suddenly and completely, with the idea fully formed that if the vagus nerves inhibit the heart by liberating a muscarin-like substance, the substance might diffuse out into a salt solution left in contact with a heart while it was subjected to vagal inhibition, and that then the presence of this substance might be demonstrated by inhibiting another heart through the influence of the altered solution. He scribbled the plan of the experiment on a scrap of paper and went to sleep again. Next morning, however, he could not decipher what he had written! Yet he felt that it was important. All day he went about in a distracted manner, looking occasionally at the paper, but wholly mystified as to its meaning. That night he again awoke, with vivid revival of the incidents of the previous illumination, and after this experience he remembered in his waking state both occasions. He set up a frog heart filled with Ringer's fluid, and after inhibiting the heart by stimulating the vagus nerve, found that the fluid had acquired a new property—that of being able to induce in another frog heart typical inhibitory vagal effects. Furthermore, he found also that when the sympathetic nerves were stimulated, to make the heart beat more rapidly, the Ringer solution in contact with it became endowed with cardio-accelerator power, *i. e.*, an agent was added to it, which, like adrenin, had sympathomimetic influence.¹⁶ Although, at first, these observations were not confirmed by some investigators, they have been wholly substantiated by others, and at present the support for Loewi's work may be regarded as conclusive.

The nerves supplying the heart are representatives of the widely distributed fibers of the parasympathetic and sympathetic divisions of the autonomic system. The question naturally arises, can the phenomena noted in the heart be repeated elsewhere in the body?

That has been found to be true. Stimulation of smooth muscle and likewise glands causes the appearance of sympathomimetic and parasympathomimetic substances in neighboring fluids. Thus, Engelhart¹⁷ noted that after he had excited electrically the oculomotor nerve and induced contraction of the smooth muscle of the ciliary body and the iris, the aqueous humor of the eye had a new vagus-like action on the tortoise heart. Furthermore, Bain¹⁸ has reported that fluid flowing through the bloodvessels of the tongue of a dog, while the smooth muscle of the vessel walls was being relaxed by exciting the lingual nerve, was endowed with the ability to provoke activity in the smooth muscle of the rabbit intestine. And finally, Gibbs and Szelöczy¹⁹ have demonstrated that the perfusing fluid, which has passed through the vessels of the cat's submaxillary gland during periods of stimulation of the chorda tympani nerve, can cause a fall of blood pressure, excitation of a salivary flow, inhibition of the isolated frog heart and augmented intestinal movements. In all these instances the structures were originally affected by parasympathetic nerves, and the salt solutions in contact with the structures were made capable of producing characteristic parasympathetic effects on other structures. The analogy with Loewi's frog heart experiments is evident.

Similar evidence extended in the sympathetic system Loewi's original evidence of chemical transmission of nerve impulses. Thus Brinkman and Van Dam,²⁰ Külz,²¹ and also Lanz²² found that the Ringer solution from a heart which has been accelerated by sympathetic stimulation exerts a typical sympathetic inhibitory effect on gastric peristalsis—just the sort of effect that is produced by injection of adrenin. Furthermore, Finkelman²³ showed that if Ringer's solution is allowed to run over a pulsating strip of rabbit intestine still supplied with its mesenteric nerves (piece A), and to drop thence on another strip of pulsating intestine (piece B), the solution has a new property, as piece A is inhibited by nervous stimulation—then piece B on which the solution drops is also inhibited.

In all the experiments hitherto cited, except those of Uridil and myself,¹³ the mode of transfer of the chemical agent that mimics the action of sympathetic or parasympathetic nerve impulses is by way of salt solutions. This condition was criticized in 1929 by Demoor,²⁴ the Belgian physiologist, who pointed out that the irrigations which are part of the methods employed "may create new conditions of existence for the tissues, conditions accompanied by permeabilities which do not exist in physiologic states, and that the escape of vagal and sympathetic substances, though proved experimentally, may not occur normally." This prudent skepticism has been met by evidence that the substance representing parasympathetic impulses can circulate in the blood under nearly normal conditions, and that the substance representing sympathetic impulses can circulate under conditions which are wholly normal.

In order to understand this advance we must consider first the nature of the so-called "vagus substance." Studies by Loewi and others²⁵ have shown that it is dialyzable, that it is stable in an acid but not in an alkaline medium, that it is rapidly rendered inactive by a blood or tissue esterase, and that, if thus altered, the activity can be restored by acetylation. In all these respects the vagus substance is like acetylcholin—a fact that recalls Dale's observation in 1914, that acetylcholin mimics the functions of parasympathetic impulses. Another feature common to vagus substance and acetylcholin is that each is protected from inactivation by physostigmin. The rapid destruction of the substance in blood can thus be largely avoided. Such was the strategy employed by Babkin, Alley and Stavrocky²⁶—during each experiment they injected physostigmin repeatedly in doses sufficient to assure success. With that provision they found that when they caused, say, the left submaxillary gland to secrete by stimulating its chorda tympani nerve, they obtained slightly later a secretion from the right submaxillary gland, which had been denervated. The only means of communication from one gland to the other was the circulating blood; and when the vein conveying blood from the stimulated gland was closed, repetition of the stimulus did not produce its regular effect on the other side. Not only secretion, but also dilation of the blood vessels on the denervated side was recorded, and attendant thereon was a fall of blood pressure. All these results are characteristic of both parasympathetic discharge and the action of acetylcholin. They not only support the other evidence that when parasympathetic nerves are excited they produce their effects by liberating a mediating substance, but also they show that this substance, protected by physostigmin, can be carried without destruction in the circulating blood, and can mimic elsewhere in the organism the effects of parasympathetic impulses.

The observations of Babkin and his collaborators were published in 1932. In 1931, Bacq and I²⁷ reported that a substance mimicking the effects of sympathetic impulses was carried in the blood stream from a stimulated region and could produce typical adrenin-like effects elsewhere. This result solved a mystery which had puzzled workers in our laboratory for some years. In order to make this part of the story clear, I must return again to the controversy with Stewart and Rogoff, previously referred to.

The Cleveland investigators had declared that the secretion of adrenin from the adrenal medulla is steady and unvarying, whereas our group contended that asphyxia, "painful" stimulation and emotional excitement cause a special discharge of adrenin. Each side brought out supporting evidence, but evidence obtained by different experimental procedures. In order to secure more facts bearing on the controversy, Lewis, Britton and I²⁸ devised a method of separating the heart surgically from the central nervous system while leaving the organism otherwise in a quite normal state. The

heart in these circumstances, though not subject to nervous control, may be strikingly influenced by changes in the circulating blood. For example, it is exquisitely sensitive to an extremely minute increase in the concentration of adrenin. By use of the denervated heart it was possible to prove that asphyxia and "painful" stimuli, and also motion and emotion, induce medulli-adrenal secretion, for the faster heart rate evoked by these states fails to occur after the adrenal glands are rendered inactive. Thus, before adrenal inactivation, emotional excitement with attendant struggle might cause a high rise in the pulse rate—100 beats per minute or more—beginning within a few seconds from the start of the struggle; but after the inactivation, this quick, sharp rise almost wholly disappeared. I shall not detail further the evidence for special secretion of adrenin; it is sufficient to remark that after many years no one has confirmed the results reported by Stewart and Rogoff, and that numerous investigators, using various methods, have found, as we did, that medulli-adrenal secretion is influenced by any situation which calls the sympathetic system into activity.

Now, although the quick, sharp rise in the rate of the denervated heart was absent after the adrenal glands could no longer participate in the response, there was a slow, moderate increase of the rate. Shortly after a brief excited struggle, for example, the rate began to be faster, and at the end of about 3 minutes it might be elevated by 25 or 30 beats per minute. This strange phenomenon, first noted in 1926, remained for years unexplained. What was the cause of it? In the efforts to find an answer to that question I was ably helped by Newton and Zwemer.²⁹ We perceived clearly that the phenomenon must have been due to some change in the circulating blood, for that alone connected the heart functionally with the rest of the organism. Previous experiments had proved that it did not result from increased blood pressure, from increased blood temperature, nor from metabolites thrown off by active muscles. It seemed most probably the effect of some internal secretion. Successively we removed not only the adrenal medulla but also accessory chromaffin tissue lying between the kidneys, we ruled out the adrenal cortex, we set aside the liver by severing the hepatic nerves, we excluded a possible rôle of the alimentary canal by extirpating the abdominal sympathetic chains—and still struggle made the heart respond in a more rapid pulse. We removed the pituitary body, we disconnected the thyroids and parathyroids from the spinal cord by taking out the cervical sympathetic strands—and still the mysterious acceleration persisted. Though much puzzled by the situation we treasured the certainty that excitement and struggle cause discharge of sympathetic nerve impulses. At the stage now reached in our efforts to solve the riddle, only short strands of the sympathetic were still present—the remnants in the lower thorax. Might it not be true that impulses discharged *via*

these few ganglia were somehow causing the heart to beat more rapidly? We removed them—and the strange cardiac acceleration ceased! Vigorous struggle sent the beat up perhaps 4 beats per minute, but not 25 or 30. Observe that we now had a new organism in the history of biology—a higher vertebrate without any sympathetic system. Interest in the altered physiology of such a creature temporarily turned our attention away from the curious, slow cardio-acceleration which we had started to investigate, and not until 1930 was that trail sought again and followed.

That the remnants of the sympathetic ganglia in the lower thorax distribute fibers to the liver or the heart seemed quite improbable. It appeared more likely that when they discharged impulses into the skin region they produced something which entered the circulating blood and affected the heart.

In order to test this idea Bacq and I²⁷ prepared animals with denervated hearts, and then stimulated the lower abdominal sympathetic chains, isolated from the spinal cord. These chains innervate only smooth muscles—those of the hairs and the blood vessels, especially in the region of the tail. Of course the only functional connection between the denervated tail and the denervated heart was the vascular system. We found that when we stimulated the sympathetic chains and caused erection of the tail hairs, there followed in about 2 minutes a marked elevation of arterial blood pressure and in about 3 minutes an increase of heart rate of 18 beats per minute. When the bloodflow into and out from the tail was blocked the same stimulus had no effect, until the block was removed. We found, further, that when we stimulated sympathetic nerves to smooth muscle elsewhere, *e. g.*, in the abdomen, we could produce the same effects on the denervated heart and on other denervated structures. Thus the submaxillary gland and the nictitating membrane could be rendered active by exciting the splanchnics after severance of the liver nerves and removal of the adrenal glands. The conclusion drawn from these experiments was that such excitation causes the affected cells to liberate a substance into the blood stream and that this substance, carried elsewhere in the body, may have effects similar to sympathetic impulses. It is worthy of emphasis that the phenomenon occurs under quite normal conditions and that no drug—analogue to physostigmin—is required to make it obvious. Previous investigators, who had found a sympathomimetic substance in salt solution which had been in contact with structures stimulated through sympathetic nerves, called it “sympathetic substance.” In place of this cumbersome expression we suggested the name *sympathin*.

The most recent chapter in this story, first told last year, is concerned with the nature of sympathin. In many respects sympathin resembles adrenin. Like adrenin it causes, as we have seen, a faster heart beat, a rise of arterial blood pressure, an increased flow of

saliva (in the cat), and a contraction of the nictitating membrane. Furthermore, as Bacq³⁰ has shown, adequate liberation of sympathin may increase blood sugar, inhibit the rhythmic movements of the intestine, shorten the *retractor penis* muscle, contract the spleen, relax the cat's non-pregnant uterus and dilate the pupil. In all these respects sympathin seems to be indistinguishable from adrenin. And this testimony from similar biologic reactions is in accord with testimony from chemical studies. In applying a modified Viale test, sensitive to adrenin 1 to 30,000,000, Bacq³¹ found the intensity of the color change greater, in the aqueous humor of the eye and in the fluids from a skin vesicle after the sympathetic nerves to the parts had been excited, than it was before. The color change, though not specific for adrenin, indicates that the chemical structure of adrenin and that of some substance produced by sympathetic impulses (sympathin) are alike. After all this evidence had accumulated we naturally inferred, as others also had inferred, that sympathin was simply adrenin produced locally in the responsive cell on the arrival of nerve impulses, as Elliott suggested 30 years ago. Last year, however, Rosenbluth and I³² found that sympathin and adrenin are different.

The discovery came about in this way. We were looking for further resemblances between the two substances—adrenin and sympathin. Dale had shown, in 1906, that the drug ergotoxin blocks the influence of adrenin on vessels constricted by sympathetic impulses, while leaving unaffected vessels dilated by such impulses. After an appropriate injection of ergotoxin, therefore, adrenin, instead of causing a rise of blood pressure, causes a pure *fall*. Is the action of sympathin affected by ergotoxin in a similar manner? was the question we asked. We administered to an animal under anesthesia a proper amount of ergotoxin, proved that adrenin caused a fall of pressure, and thereupon stimulated the sympathetic fibers leading to the hind legs and the tail. To our great surprise the blood pressure, after an immediate slight fall, entered a prolonged rise; and hepatic nerve stimulation, such as Uridil and I had employed in 1921, produced a *pure rise*. Clearly sympathin and adrenin are not exactly the same. If they were, they would act the same.

The difference seemed to be expressed by an inability of sympathin to induce relaxation after ergotoxin. We then noted that in producing sympathin we had been stimulating regions (the liver and the tail) in which by sympathetic impulses we produced *contraction*. What would happen if, instead, we produced relaxation? We decided to try out that idea on different organs, contracted or relaxed by adrenin, and to avoid ergotoxin. To that end we selected as *indicators* the denervated nictitating membrane as an organ contracted by adrenin, and the denervated non-pregnant cat uterus as an organ relaxed by adrenin. As a *source* of what may be

called "contractile" sympathin we selected the liver. We found, to our great interest, that when the hepatic nerves were stimulated, the nictitating membrane contracted, but the uterus, though highly sensitive to adrenin, failed to relax. Recall that hepatic nerve stimulation, after ergotoxin, caused a pure rise of blood pressure, as if the sympathin which was given off had only a contractile effect. If the nerves on the duodenohepatic artery are stimulated, however, they produce two effects—*contraction* of smooth muscle in the blood vessels of the liver and duodenum and *relaxation* of smooth muscle in the duodenal wall. In these circumstances we found that not only does the nictitating membrane contract, but the uterus relaxes. Now if the nerves to the duodenum are severed and the same stimulus as before is applied to the nerves on the duodenohepatic artery, only contraction of the nictitating membrane results.

From these and accessory experiments Rosenblueth and I suggested that there are two kinds of sympathin—sympathin E, given off from smooth muscle which is excited to contract by sympathetic impulses, and sympathin I, from smooth muscle inhibited or relaxed by such impulses. Escaping from the cells of origin, sympathin E, borne by the circulating blood, is able to cause contraction in distant smooth-muscle organs which contract in response to sympathetic excitation; and sympathin I, analogously, affects smooth-muscle organs which relax.

The results just described have a direct bearing on the ideas expressed by Langley in 1905. Remember that he assumed that two different receptive substances, excitatory and inhibitory, exist in cells affected by adrenin, and that the different effects of that agent in different regions are due to the difference of these two substances. Researches by Rosenblueth³³ connect our results with Langley's ideas. Rosenblueth injected adrenin in gradually increased doses and found that the degrees of response of various viscera, when plotted, fell into a typical hyperbolic curve, the curve indicating chemical union. The inference was drawn that the adrenin, A, unites with a hypothetical substance, H, making AH, before it becomes effective. A similar hyperbolic curve resulted when maximal shocks were applied with increasing frequency to the sympathetic nerves which supply the same viscera. Again the evidence indicated that the mediator, M, set free in the cells by the nerve impulses, unites with a hypothetical substance, H, before acting. The experiments which led us to conclude that two kinds of sympathin exist, have led us to assume, further, that the hypothetical substance, H, must be separated into two distinct substances, E and I. Then M, the primary chemical mediator, when united with E, would become sympathin E; and when united with I, sympathin I. And ME and MI would have the same effects on remote smooth-muscle cells, which they enter from out-

side, as they have in the cells in which they originate. Thus Langley's insight appears to be substantiated by facts.

It is noteworthy that sympathin, the chemical representative of sympathetic impulses, is much more stable than acetylcholin, the representative of the parasympathetic impulses. Whereas the former can readily be shown not only to be present in circulating blood but to coöperate with adrenin, and to have widespread effects in the body, the demonstration of acetylcholin in the circulation is difficult and requires specially devised conditions to prolong its normally brief existence. This striking difference between the two mediating substances is quite in harmony with evidence as to the difference of neural organization of the sympathetic and the parasympathetic divisions of the autonomic system. The sympathetic neurons are organized for diffuse discharge of their impulses throughout the organism, to produce related adjustments of bodily processes—a provision favored by coöperation of sympathin and adrenin simultaneously set free in the blood stream and acting, therefore, diffusely. The parasympathetic neurons, on the other hand, are arranged for specific effects on separate organs—contraction of the pupil, for example, and slowing of the heart. These effects are quite unrelated. If acetylcholin were a persistent agent in the blood, it might bring about temporally related changes in biologically unrelated phenomena. Fortunately that result is avoided by the extreme instability of the mediator of parasympathetic impulses.

In following the records up to this point I have mentioned only the humoral agents manifested when the autonomic system acts upon cardiac and smooth muscle and on certain glands. The reason for that selection was that in those respects the historical sequence of ideas and evidence could be clearly traced, step by step, in a way that seemed to me interesting and possibly illuminating. Another similar movement, somewhat aside from this main current but in the same direction with it, has been the development of evidence that the chromatophores of both vertebrates and invertebrates are under chemical control. Time does not permit, on this occasion, even a brief report of the ingenious experiments which have led to that conclusion. In Parker's³⁴ little volume will be found an admirable and entertaining account of that aspect of recent progress.

At the outset I said that the story of our gradual understanding of the chemical mediation of nerve impulses would lead us to the point where we could look forward to new triumphs of physiologic investigation. That fair prospect lies in the direction of the nervous system. Certain characteristic features of reflexes include a failure of a single afferent impulse to evoke a response, whereas repeated impulses are effective; and also a continuation of the response for some time after the stimulus has ceased to act—the so-called "after

discharge." About 9 years ago Sherrington³⁵ suggested that a more or less persistent central excitatory state (or a central inhibitory state), without a refractory period and subject to summation, might explain these phenomena. It was assumed that repeated impulses could build up the state in a center until it became capable of discharging efferent impulses, or it could be built up to such a degree by rapidly repeated, strong stimulation that it would continue to discharge for some time before returning to the resting condition. Later Fulton³⁶ substituted "substance" for "state," and the concept of central excitatory or inhibitory *substance* was expounded, a concept at once related to the peripheral mediation of nerve impulses, with excitatory and inhibitory attachments, that we have been considering. Some quite recent researches have given support to the reasonableness of the idea that between the neurons of the nervous system, as well as between outlying autonomic neurons and their effector organs, chemical agents of transmission intervene.

Last year Kibjakow,³⁷ a Russian investigator, published important observations made on the perfused superior cervical sympathetic ganglion of a cat. While the salt solution was running through the bloodvessels of the ganglion, he stimulated the related cervical sympathetic strand, causing thereby, of course, contraction of the nictitating membrane. He found that the perfusate, when later passed through the blood vessels of the ganglion, had no effect if it came away before or after the stimulation; but if it came away during the stimulation it showed signs of having acquired a new property, for it now caused a contraction of the nictitating membrane. In short, some substance conveyed in the fluid had the same effects as the nerve impulses. Since Kibjakow's experiments were reported Feldberg and Gaddum,³⁸ working in Dale's laboratory, have brought forward evidence that in the transfer of nerve impulses from neuron to neuron in sympathetic ganglia, a chemical agent appears and that this agent is acetylcholin.

Meanwhile Rosenblueth³⁹ published a research in which he studied the effects on the heart of discharge from accelerator and inhibitor centers when these centers are affected by increasing frequencies of maximal stimuli applied to their afferent nerves, just as he had previously studied the effects on smooth muscle when stimulated through its nerves. The resulting changes in heart rate could be plotted in a rectangular hyperbola similar to that for smooth muscle—a resemblance indicating that the reflex output from the centers is directly proportional to the excitatory input. This linear relation between input and output could be explained without invoking chemical intervention in the conducting process. The *duration* of the output from the centers, however, is hard to account for in other terms than those of chemical mediation. As the frequency of the maximal efferent impulses was increased the persistence of

the reflex effects became longer and longer—indeed; in some instances not subsiding before a lapse of 10 minutes! When the peripheral nerves of the heart were stimulated, the recovery of the former rate was prompt. It is clear, therefore, that some change induced in the centers, no matter whether excitatory or inhibitory, persists for a long period and throughout the period continues the discharge of nerve impulses. The hypothesis that explains the results better than any other is that the central change is chemical in nature.

At this point one can let one's imagination play. It seems not improbable that a great new realm of physiologic research is opening before us, research which will disclose the mode of operation of the most mysterious part of the organism, the central nervous system. We may soon have proof of chemical mediation in central nervous processes, and know what the mediator is. As time goes on we may be able to tell in chemical terms why sometimes the processes are retarded, sometimes greatly accelerated. In the future we may be able to apply to the nervous system the ideas worked out on smooth muscle, and realize that the depression of manic-depressive state results from excess of inhibitory substance at some region in the brain, while the excitement means excess of the excitatory substance. But such dreams are only too easy. Cautious progress, step by step, is the safer mode of progress. And in the future, as in the past, carefully controlled experiments—experiments in which lower animals will be humanely employed—will be the most important means of advancing our knowledge.

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ON THE INHERITANCE OF DIABETES MELLITUS.

II. FURTHER ANALYSIS OF FAMILY HISTORIES.

BY GREGORY PINCUS, Sc.D.,

ASSISTANT PROFESSOR OF GENERAL PHYSIOLOGY, HARVARD UNIVERSITY, BOSTON, MASS.,
AND

PRISCILLA WHITE, M.D.,

PHYSICIAN, NEW ENGLAND DEACONESS HOSPITAL,
BOSTON, MASS.

(From the Laboratory of General Physiology, Harvard University, and the George F. Baker Clinic, Elliott P. Joslin, M.D., Medical Director, at the New England Deaconess Hospital.)

The Necessity for a Correction in the Mendelian Expectation of Diabetes. A first analysis of the possible basis of the hereditary transmission of diabetes mellitus (Pincus and White^{1,5}) dealt with the probability that a single recessive gene was the genetic factor concerned. The overwhelming proportion of traits ordinarily subjected to genetic analysis are identifiable at birth or shortly thereafter. Albinism, for example, is an immediately and easily observable condition, and the problem of its inheritance requires merely the examination of the proportions of albino and non-albino individuals in various types of matings, and the determination of the conformation of these ratios to any particular theory of the inheritance of albinism. Diabetes, on the other hand, is a condition which is definitely not identifiable immediately, but one which is manifested in different individuals at different ages. The ordinary age-incidence statistics indicate that certainly not until age 90 is

reached will every potential diabetic develop definite symptoms of the disease. Accordingly, if the analysis of the inheritance of diabetes were to be made completely similar to the analysis of the genetics of albinism, it would be necessary to examine families every member of which had lived to age 90 or beyond. In all the family histories that we have collected we have not found a single one that satisfies this condition. It became necessary, therefore, to construct a correction to the simple Mendelian expectation. This correction was calculated by assuming that every potential diabetic before developing the disease was subject to the ordinary chances of death, and then obtaining for every decade of life the percentage of potential diabetics actually developing the disease by applying the ordinary life-table expectancies to the best available statistics of diabetes incidences.

Material and Methods. It will be noted that we assumed that "ordinary" life table expectancies apply to diabetics before they develop the disease. When these expectancies taken in our previous analysis (Glover, U. S. registration area for 1910) were applied to the age-incidence data for diabetes collected by Joslin over the period 1898 to 1926, an estimate of the proportion of potential to identified diabetics was obtained for each decade of life. No attempt was made to justify the use of the 1910 life tables except by the statement that they must apply roughly to the incidence data collected over the stated period of years. Our population of diabetic families contained certain persons exposed to the chances of death existing during the 19th century, other persons exposed to the 1933 risks, and between these two extremes various persons exposed to the risks of intervening periods.

We have examined the questions of what sort of life tables might apply, and whether the application of any particular set of life expectancies is preferable or justifiable in obtaining the corrections, or whether the employment of any reasonable life table gives us the general result our Mendelian hypothesis would demand. The results indicate that as long as persons die in the rather regular manner indicated by the usual life table, and as long as diabetes develops with the usual frequencies per decade, the expectation of diabetes in diabetic families satisfies as well as can be expected the hypothesis that the development of diabetes is dependent on the transmission of a single recessive gene. We may note that the analysis which follows makes no pretense to great statistical refinement, chiefly because the limitations of the available data would make great refinement misleading and pretentious.

Our calculations of incidence are based upon Joslin's records taken on 9853 patients, from the years 1898 to 1933, inclusive. These data represent the most extensive series now available to us. They are usable only if they give a fairly accurate picture of the ordinary age incidence of diabetes. Fortunately they are derived from a practice which deals with diabetics of all ages, and is not concerned with diabetes in any particular age group, with the possible qualification that cases appearing in recent years *might* contain a slight excess of younger diabetics.

It happens that Joslin's data differ from the general statistics of diabetes incidence based upon mortality (Pincus, Joslin and White⁶). This is true even if the mortality statistics are corrected for the presumed duration of the disease. (Tables 1 and 2.) We, therefore, employ the Massachusetts data on deaths due to diabetes, and correcting them for duration (on the basis of the duration data given by Joslin²) we set up a second set of inci-

dence data differing markedly from Joslin's in order to ascertain the alteration in Mendelian expectations that would ensue. The Massachusetts data were collected over roughly the same period that Joslin's data were collected. It is necessary, in order to apply these data, to construct age specific rates of diabetes onset in a population having the same general age distribution as our diabetic families. A careful analysis of the mortality rates among the children of these families shows that the 1920 mortality rates apply with moderate accuracy. Accordingly we derive Tables 1 and 2, which present life tables based on mortality rates corresponding rather closely to those of 1920, but sufficiently modified to approximate the life expectations required by our observed population of children. We employ a smoothed life table rather than one that can be derived from our population of children chiefly because it is scarcely possible to adjust for the great excess of deaths due to diabetes in our data; but also in order to approximate with some reasonableness the presumed population from which our general onset data are derived. These tables are, therefore, only approximate, and the expectancies derived from them cannot be used for any exact tests of significance. None the less they are necessary for two purposes: (1) To ascertain the presumable number of genetically diabetic parents, and (2) to obtain a correction to our Mendelian probability of genetically diabetic individuals among the children.

Before proceeding to any analysis of the population of children it is necessary to determine the genetic nature of the matings that produced them. We designate a genetically diabetic individual by the symbol *mm*. Since each of the matings employed in our analysis produced at least 1 diabetic child, the possible parental combinations are: (1) $Mm \times Mm$, (2) $Mm \times mm$, (3) $mm \times mm$. Every diabetic parent we can classify at once as *mm*. But our incidence tables tell us that a number of potential diabetics will die before they exhibit symptoms of diabetes. The problem is to determine how many of such individuals exist among our parents, and, furthermore, how many of the living parents are potential diabetics. Since we know nothing of the matings which produced these parents we can only approximate this number. This is done by assuming that the observed numbers of diabetic parents represent a certain proportion of the total number of potential diabetics in the parental population. It happens that these parents are a particularly long-lived group of persons, so that the mortality rates of our incidence tables do not apply particularly well until the 7th decade is reached; and, since, according to Table 1, the 6th decade is the decade of maximum incidence, there is exceptional opportunity for diabetes onset among the parents. Even on the basis of the data of Table 2 (where the 7th decade is the decade of maximum incidence) the low early mortality rates should give us an exceptionally large number of recognized diabetics among the parents. Assuming then that the observed diabetic parents in each decade represent that proportion of the total number given by our incidence tables, we calculate on the basis of Table 1 (correcting for the presence of a small number of living parents) that there are in the parental population an average of about 63 potential male diabetics and 95 potential female diabetics, which leaves respectively 5 male parents and 7 female parents or a total of 12 potentially diabetic parents unidentified.* Similarly, on the basis of the data of Table 2 there are 175 potentially diabetic parents unidentified.

* The 4 diabetic male parents appearing in Decade 4 (Table 6) are taken as 7.12% (see Table 1, Column 4) of the total that were alive at the beginning of that decade. Therefore, 56 potential diabetics were alive at age 30. The total number of male parents identified is 58, or 2 more than expected. We go through the table of parents in a similar way, decade by decade, and so arrive at a rough estimate of missing *mm* parents.

TABLE 1.—LIFE TABLES FOR POTENTIAL DIABETICS ACCORDING TO JOSLIN'S INCIDENCE DATA.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Decade.	No. identified (per 100 born alive).	No. dying before identification (per 100 born alive).	No. unidentified alive at beg. of decade.	No. identified during decade as % of no. alive at beg.	No. dying during decade as % of no. alive at beg.	No. identified (per 100 born alive).	No. dying before identification (per 100 born alive).	No. unidentified alive at beg. of decade.	No. identified during decade as % of no. alive at beg.	No. dying during decade as % of no. alive at beg.
	♂-ox	♂-dx	♂-1x	♂-ox 1x	♂-dx 1x	♀-ox	♀-dx	♀-1x	♀-ox 1x	♀-dx 1x
1	1.76	12.67	100.00	1.76	12.67	1.42	10.58	100.00	1.42	10.58
2	2.91	2.93	85.57	3.39	3.42	2.25	2.06	88.00	2.57	2.35
3	4.04	3.85	79.73	5.06	4.82	3.19	4.35	83.69	2.64	5.24
4	5.98	4.68	71.84	8.32	6.51	4.28	5.11	77.15	5.54	6.53
5	11.91	4.99	61.18	19.44	8.16	11.91	5.00	67.76	17.57	7.30
6	15.90	5.50	44.28	35.88	12.42	20.81	5.69	50.85	40.89	11.19
7	11.69	5.12	22.88	51.01	22.32	13.64	4.86	24.35	55.95	19.90
8	3.57	2.22	6.07	58.33	36.36	3.46	2.04	5.85	58.67	34.69
9	0.12	0.16	0.28	37.50	62.50	0.17	0.18	0.35	38.46	46.15
Totals . . .	57.88	42.12	60.13	39.87

TABLE 2.—LIFE TABLES FOR POTENTIAL DIABETICS ACCORDING TO MASSACHUSETTS MORTALITIES CORRECTED FOR DURATION.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Decade.	No. identified (per 100 born alive).	No. dying before identification (per 100 born alive).	No. unidentified alive at beg. of decade.	No. identified during decade as % of no. alive at beg.	No. dying during decade as % of no. alive at beg.	No. identified (per 100 born alive).	No. dying before identification (per 100 born alive).	No. unidentified alive at beg. of decade.	No. identified during decade as % of no. alive at beg.	No. dying during decade as % of no. alive at beg.
	♂-ox	♂-dx	♂-1x	♂-ox 1x	♂-dx 1x	♀-ox	♀-dx	♀-1x	♀-ox 1x	♀-dx 1x
1	1.18	11.58	100.00	1.18	11.58	0.83	9.62	100.00	0.83	9.62
2	1.72	3.10	87.42	1.97	3.55	1.22	2.49	89.55	1.36	2.78
3	2.35	3.28	82.42	2.85	3.98	1.48	3.80	85.84	1.72	4.43
4	5.35	4.77	76.79	6.97	6.21	2.85	5.22	80.56	3.54	6.48
5	5.23	5.25	66.67	7.84	7.87	6.49	5.28	72.49	8.95	7.28
6	9.98	6.91	56.19	17.76	12.30	11.60	6.64	60.72	19.10	10.94
7	10.03	9.00	39.30	25.52	22.90	11.67	8.81	42.48	27.47	20.74
8	7.04	8.88	20.27	34.73	43.81	8.20	9.05	22.00	37.27	41.14
9	1.23	3.12	4.35	28.28	71.72	1.46	3.29	4.75	30.74	69.26
Totals . . .	44.11	55.89	45.80	54.20

Results. On the basis, then, of Joslin's incidence data we may consider practically all the matings of non-diabetic by non-diabetic as $Mm \times Mm$ and the matings of non-diabetic by diabetic as $Mm \times mm$. Distributing among the non-diabetic parents the 175 unidentified potential diabetic parents derived from the Massachusetts incidence tables, we arrive at 159 genetically mm parents in the non-diabetic by non-diabetic group and 16 genetically mm parents in the non-diabetic by diabetic group.

Considering now the children in these matings, we observe the age grouping (Table 3). The problem we must set ourselves is

TABLE 3.—TABULATION OF CHILDREN ACCORDING TO AGE IN THE VARIOUS MATINGS.

Decade.	Neither parent diabetic.						One parent diabetic.					
	Patients (diabetic).		Non-diabetic siblings.		Diabetic siblings.		Patients (diabetic).		Non-diabetic siblings.		Diabetic siblings.	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1	36	26	148	143	1	2	1	2	30	25	1	1
2	38	48	100	80	6	4	4	1	5	9	2	1
3	27	28	144	129	1	1	6	8	19	28	2	1
4	27	39	130	133	6	5	9	12	36	30	2	2
5	44	83	147	191	10	5	13	23	44	59	4	6
6	67	97	218	208	18	10	14	21	38	43	10	7
7	43	64	150	156	5	13	2	8	30	24	1	4
8	88	9	73	59	3	7	..	2	9	7	1	3
9	5	7	1	2
Totals	290*	394	1115	1106	51	47	49*	77	211	215	23	25

* The age at onset of diabetes of 1 patient was unknown.

this: What is the probability of identification of diabetics in the populations observed in these two types of matings? According to Tables 1 and 2 we can, in a *completed* population of potential diabetics subject to the mortalities of these tables, identify at most respectively 57.88% and 44.11% of the potential male diabetics born alive and 60.13% and 45.8% of the potential female diabetics born alive (Columns 1 and 6). The populations of children are, however, not completed since most of them are, in fact, still alive. We obtain an estimate of the proportions that should be identified, however, by the use of Columns 4 and 9 of these two tables. When this is carried through using Table 1, we determine that in the matings of (I) non-diabetic by non-diabetic 36.8% of the potential male diabetics born alive should be identified and 39.2% of the potential female diabetics. In the matings of (II) non-diabetic by diabetic the proportions are 38.7% of the males and 41.2% of the females. This gives us a mean probability of identification of 38% in matings (I) and 40% in matings (II). Similarly, employing the expectancies of Table 2 the mean probability of identification is 23% in (I) and 24% in (II). In Tables 4 and 5 we present the expectations derived by employing these probabilities. Thus in $Mm \times Mm$ families the simple Mendelian probability (p^1) is $\frac{1}{4}$ and the probability of identification as diabetic of mm individuals (p^{11}) is $\frac{3.8}{100}$ (on the basis of Table 1), giving us a probability of identified diabetics of $\frac{9.5}{100}$ (c. g., $\frac{1}{4} \times \frac{38}{100}$). In order to correct for the fact that these families were observed because at least 1 child

TABLE 4.—THE EXPECTED AND OBSERVED NUMBER OF DIABETICS IN MATINGS OF 2 NON-DIABETIC PATIENTS.

Family size by No. of children.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Totals.
No. of patients	62	104	118	113	98	67	45	31	20	16	4	4	1	2	685
Total No. of children	62	208	354	452	490	402	315	248	180	160	44	48	13	28	3004
No. of diabetic children	62	116	134	127	111	85	53	38	28	20	4	5	1	33	783
No. of diabetic children expected*	62	109.18	129.95	130.27	118.38	84.66	58.09	42.80	28.72	24.06	6.27	6.53	1.70	3.48	806.09
No. of diabetic siblings	(2)	107.83	126.76	125.85	112.95	80.11	55.76	39.60	26.55	21.87	5.08	5.86	1.39	2.86	775.07
No. of diabetic siblings expected*	(1)	0	5.18	11.95	15.27	20.38	17.66	13.09	11.80	8.72	2.27	2.53	0.70	1.48	121.09
No. of diabetic siblings observed	(2)	0	3.83	8.76	12.85	13.11	10.76	8.60	6.55	5.87	1.68	1.86	0.39	0.86	90.07
No. of diabetic siblings observed	0	8	16	14	13	18	8	7	8	4	0	1	0	1	98

* The numbers in parentheses refer to expectancies derived from Tables 1 and 2 respectively.

TABLE 5.—THE EXPECTED AND OBSERVED NUMBER OF DIABETICS IN MATINGS OF 1 DIABETIC BY A NON-DIABETIC.

Family size by No. of children.	1	2	3	4	5	6	7	8	9	10	11	12	Totals.
No. of patients	7	23	30	19	12	10	14	9	8	4	0	1	127
No. of children	7	46	60	76	60	60	98	72	72	40	0	12	603
No. of diabetic children	7	26	23	28	21	17	20	18	10	4	0	1	175
No. of diabetic children expected (1)	7	25.55	24.59	25.74	71.84	16.27	24.78	22.07	16.63	8.96	0	2.58	192.01
No. of diabetic children expected (2)	(2)	7	24.69	23.06	15.93	13.88	20.99	14.15	13.34	7.59	0	1.77	165.67
No. of diabetic siblings expected (1)	(1)	0	2.55	4.59	6.74	5.84	6.27	10.78	8.63	4.96	0	1.58	63.43
No. of diabetic siblings expected (2)	(2)	0	1.69	3.06	4.27	3.93	6.99	5.15	5.34	3.59	0	0.77	38.67
No. of diabetic siblings observed	0	3	3	9	9	7	6	9	2	0	0	0	48

(*e. g.*, the patient) was present, we employ the formula $\frac{p}{1 - (q)^n}$ to obtain our final probability, where p is the probability of identifying as diabetic an *mm* individual, q the probability that identification will not be made, and n the number of children in the family. Thus in families of 3 children the final probability is $\frac{0.095}{1 - (0.905)^3}$ or 0.3671 (*e. g.*, 36.71% of the children in families of 3 should be identified as diabetic). Strictly, we should determine the probability of identification (p^{11}) separately for each group of families of the various sizes. We have not done this because separate life tables for the various-sized families are not justified by the meager data then assembled, and because our probability tables for identification (Tables 1 and 2) are at best approximations. If we did set up the separate p^{11} for these matings according to family size some of the discrepancies in Tables 4 and 5 would disappear; the p^{11} for families of small size would be higher than 0.38 or 0.23 in $Mm \times Mm$ matings, since these families contain less infantile deaths and generally longer-lived persons than the families of larger size where the large size is due in part to the listing of all children dying in infancy. This would increase the expectation of diabetic siblings in families of small size and decrease it in families of large size. The actual differences are, however, relatively small and the gross expectations arrived at represent good approximations.

The totals* requiring closest comparison are obviously those for siblings, since the patients serve merely to bring a given family into our tables. It is at once obvious that on Joslin's incidence data we have a deficiency of diabetic siblings, and on the Massachusetts data we have an excess with a somewhat closer agreement when the general incidence data are employed. This implies that Joslin's onset tables contain relatively too many younger persons, and we noted that this may be true since his practice has been largely consultative and would tend to include more severe diabetics (*e. g.*, younger persons).

Discussion. It is obvious that a fair approximation to Mendelian expectations is had with the use of two definitely different estimates of diabetes onset incidences. If we regard Joslin's data as standard, then there is a deficiency of diabetics among the children; if the Massachusetts data are used as standard, there is a slight excess of diabetic children. That the derived expectations of diabetics differ less than one would superficially expect is due to the fact that on Joslin's data the lesser number of missing *mm* parents increases the Mendelian probability (p^1) only slightly, whereas the Massa-

* We have also several matings of conjugal diabetics (*mm* \times *mm*) in these series. On the basis of Tables 1 and 2, 12.83 and 7.86 diabetics are expected among the 40 siblings; 8 diabetic siblings were observed.

chusetts tables require an increase in p^1 due to a considerable number of missing *mm* parents, but a decrease in the probability of identification among the children (p^{11}). Clearly neither the Joslin data nor the Massachusetts data can be taken as completely adequate representations of the age distribution of diabetes onset. They are necessarily approximations. In order to calculate completely accurate probabilities of identification we should have the full distribution of diabetics according to age in a large population with exact mortality rates for that population. The most complete statistics of diabetes incidence are the registrations of death due to diabetes. But we are scarcely justified in employing the diabetes mortality statistics for the construction of life tables for potential diabetics, since it is highly questionable to assume that diabetics are subject to ordinary chances of death before they *die* of diabetes. If diabetes were lethal at onset we might make such an assumption, but the extent to which diabetics are likely to die of all other causes while they are actively diabetic is unknown.

It is, therefore, notable that with the data at hand we do arrive at results indicating the consistency of our observations with a Mendelian hypothesis.

Diabetes in Non-diabetic Families. All the foregoing analyses may be objected to on the grounds that in any group of families selected at random diabetes incidence may follow the same course. We have previously presented data comparing a diabetic with a control population, and found diabetes incidence in the two to differ significantly. Our comparisons were made employing the χ^2 method. Because of the rather scant data, we employed in certain decades calculated expectancies of less than 5, and this is open to certain theoretical objections. Since our previous publication our control population has been enlarged somewhat and we are able to make more reliable comparisons. Our control population was assembled by questioning a group of non-diabetic individuals about the incidence of diabetes in their families. (Table 6.) The total incidence of diabetics among the siblings and parents of our diabetic population is 6.7%, while in the control population it is 1.23%. This difference is statistically significant, but since the incidence per decade is the obviously fairest basis of comparison we have presented the data by decades. When the χ^2 method is employed to test the independence of the two groups we combine the data for Decades 1 and 2 and 3, 4 and 5, and 8 and 9, in order to arrive at expectancies greater than 5. The value of χ^2 arrived at for the 5 groupings employed is 56.996 and this gives a value of $P > 0.000001$. In short, the chances are less than 1 in 1,000,000 that the difference between these two populations is not significant. The incidence of 1.23% that we obtain for our control population may seem rather low, but in view of the fact that it is a comparatively young popula-

tion, this incidence is understandable. We have, if anything, selected in our control group for higher incidence, since the controls were obtained by questioning 1 member of a family who was not diabetic. Obviously if diabetes occurred purely at random these controls were selected for greater than normal incidence and the diabetic group for less than normal incidence. The highest estimates of diabetes incidence seldom exceed 2.5%, and the difference between 1.5% and 6.7% is, on the basis of the numbers in our diabetic population, decidedly significant. In fact, the general incidence of diabetes would have to be a minimum of about 6% in a similar age grouping to be less than significantly different from the incidence in our diabetic population.

TABLE 6.—A COMPARISON OF DIABETES INCIDENCE IN A CONTROL AND IN A "DIABETIC" POPULATION.

Decade.	Diabetic population.				Control population.			
	Total siblings.	Diabetic siblings.	Total parents.	Diabetic parents.	Total siblings.	Diabetic siblings.	Total parents.	Diabetic parents.
1 . . .	355	5	119	0
2 . . .	208	13	100	1
3 . . .	315	5	27	...	136	0	7	0
4 . . .	352	16	171	7	134	1	25	0
5 . . .	476	28	228	16	140	0	69	0
6 . . .	560	48	277	36	114	0	96	1
7 . . .	388	23	358	55	75	3	99	4
8 . . .	166	15	330	27	35	1	87	4
9+ . . .	15	1	229	5	9	0	51	1
Totals .	2835	154	1620*	146	862	6	434	10

* 24 parents whose ages were unknown have been omitted from this table.

Secondary Factors in the Production of Diabetes. We may indicate briefly what the significance of our findings is for the etiology of diabetes mellitus. If our data be taken to indicate that the presence of a recessive gene (in double dose, *i. e.*, *mm*) is necessary for the expression of diabetes, then it is at once obvious that the problem of etiology is in one degree simplified. For the question that remains to be answered is: Given the proper genic constitution, what determines that it shall be expressed as diabetes? One or several secondary factors may be involved, but they are factors which appear in a particular manner, as the incidence-age relations indicate. The fact that we must invoke such secondary factors in no way vitiates the postulation of a primary genic cause. No genes can operate *in vacuo*, and every case of genic action is attained only with the coöperation of other agencies. These may be environmental or internal. The data presented in this paper give but meager clues as to the secondary factors. If more delicate indices of the action of the presumed gene for diabetes were available, perhaps some more definite conclusions could be drawn.

It is perhaps pertinent to indicate that modern research indicates the possibility of the action of two factors in the production of diabetes mellitus. These are the failure of the pancreas to produce the normal quota of insulin and the production of a diabetogenic hormone by the anterior lobe of the pituitary gland (Evans,¹ and Marine and Baumann³). It is known also that an endocrine function may be definitely controlled by a Mendelian recessive, *e. g.*, the marked impairment of pituitary function in dwarf mice (Snell,⁸ Smith and MacDowell⁷). In subsequent papers we may be able to consider more specifically the rôle played by the presumed gene for diabetes in relation to endocrine factors underlying manifestations of diabetes.

Summary. Among the parents and siblings of a group of diabetic patients the reported incidence of diabetics is 300 in a total of 4434 individuals (6.7%), whereas only 16 diabetics were reported in a total of 1296 parents and siblings of a group of non-diabetic patients (1.23%). The difference between the percentages observed is statistically significant. When the assumption is made that diabetes develops in individuals homozygous for a recessive gene (*i. e.*, in *mm* individuals), it can be demonstrated that the ratios of diabetic to non-diabetic individuals among the siblings of the diabetic patients conform with the consequent expectations, provided we assume that potential diabetics before they develop the disease are subject to the ordinary chances of death. Employing differing incidence data causes little variation in our Mendelian expectations. This is taken to indicate that as long as diabetes occurs in the fairly regular manner indicated by ordinary incidence tables, and as long as the chances of death indicated by the ordinary life tables apply, Mendelian expectations will be satisfied. It is, therefore, highly probable that the development of diabetes mellitus depends primarily upon the transmission of a single recessive gene. But the ordinary age-incidence relations indicate the operation of one or more secondary factors. Our data give no accurate clue to the nature of these secondary factors.

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NON-OPERATIVE VERSUS OPERATIVE MEASURES IN THE TREATMENT OF PULMONARY TUBERCULOSIS.

By F. M. POTTENGER, M.D.,

CLINICAL PROFESSOR OF MEDICINE (DEPARTMENT OF DISEASES OF THE CHEST) UNIVERSITY OF SOUTHERN CALIFORNIA SCHOOL OF MEDICINE, LOS ANGELES; MEDICAL DIRECTOR OF THE POTTENGER SANATORIUM, MONROVIA; CONSULTANT, LOS ANGELES COUNTY GENERAL HOSPITAL, LOS ANGELES; CHAIRMAN OF MEDICAL EXECUTIVE BOARD AND CONSULTANT, LOS ANGELES SANATORIUM AND EXPATIENTS HOME, DUARTE.
MONROVIA, CALIF.

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THE forces organized against tuberculosis today are pressing forward in three columns. The physicians are making a frontal attack, while the public health officials and surgeons are holding the right and left wings and pressing rapidly toward the center, where all forces, united, hope to cause a complete rout of the enemy.

At the outset of this discussion I wish to make plain that there is no antagonism between non-operative and operative measures in the treatment of tuberculosis. There is a vast difference in opinion as to when the one or the other should be employed, but such antagonisms as exist are between partisan advocates of the one or the other method. In this paper I wish to discuss the curability of tuberculosis and attempt to point out the manner in which healing is accomplished. I wish further to point out the factors which favor and those which prevent such an accomplishment, and to show how treatment must be suited to each case and further show that the correct treatment is conservative whether it be operative or non-operative.

I wish further to make plain that the particular measure which will be adopted will depend very much upon the opinion which the physician holds regarding the curability of tuberculosis, on the one hand, and its infectiousness both as far as forming metastases in the host and its danger of infecting others is concerned, on the other. He who has great confidence in its curability will be slower in interfering, while he who is imbued with the great danger of its spreading and forming new metastases, likewise he who is imbued with the great danger of infecting others, will interfere more quickly.

If patients could all be treated in an ideal environment by physicians who not only understand tuberculosis but who possess a mental attitude adapted to the treatment of chronic illness, and if the patients were so desirous of getting well that they would rigidly adhere to the necessary regimen, then the cure of early tuberculosis, like that of other infectious diseases, would be largely a matter

of natural and specific defense, and only complicating conditions would require a deviation from the well-established hygienic, dietetic, open air, rest regimen.

But such is not the case. Patients with various personalities which determine the degree of coöperation or lack of coöperation which they will give, with various domestic, social and economic problems to face, must be treated in various environments by physicians who have different conceptions of tuberculosis and personalities which endow them with different degrees of fitness for carrying out the treatment of such a chronic disease. These variants influence the success to be attained as much as the character of the treatment which is instituted to cope with the disease *per se*. Therefore, we cannot discuss the treatment of tuberculosis from a purely scientific standpoint, but must include its psychologic, social, domestic and economic aspects.

Therefore, a favorable result obtained by operative measures does not necessarily mean that it could not have been attained by non-operative measures, nor does one attained by non-operative measures mean that it could not also have been attained by operative measures. The point at issue is, which method best conserves the interest of the patient? and this can be determined only after taking into consideration and carefully weighing the dangers that may come to the patient by not using some operative measure and comparing them with any injury that may follow the employment of operative procedure.

Development of the Modern Methods of Therapy. For centuries, physicians were called only to treat patients suffering from what we now look upon as far-advanced tuberculosis. There was no organized program of treatment based on a knowledge of the disease, nor was there any accurately recorded experience on which to base opinions. Tuberculosis was not recognized as coming under public health control. It was not even classed among the reportable diseases. It was simply looked upon as an unpreventable and hopeless malady.

At the beginning of this century the entire picture changed. There was a steadily growing belief that tuberculosis could be cured and, further, that it probably could be prevented. A group of leaders with an increasing army of followers began to act upon this belief. A campaign of education ensued which was prosecuted with such zeal as had never before been witnessed in connection with any disease. Medical societies gave tuberculosis an important place on their program; public addresses were given; pamphlets were distributed; and laws were enacted to provide the measures necessary to prevent and the facilities necessary to cure the disease.

For the first time in history the medical profession began to take a real vital interest in tuberculosis. The result, the reduction

of tuberculosis to the sixth rank as cause of death, and the reduction of infection to one-half of its former amount, is one of the truly great medical triumphs. In the space of time marked by less than one-half of a generation we have so changed our attitude toward the disease, and so successfully devised methods for its prevention and cure, that we now feel that it is well on the way to be conquered or at least to be reduced to a position of importance comparable to that of other serious diseases.

As long as tuberculosis exists, however, it will be a disease of special importance, because of the fact that its prevalence is so much greater during the productive period of life than is that of most other serious diseases and, further, because of its chronicity and its slowness in healing.

Public health agencies are now spending their energies in the prevention of tuberculosis, and clinicians are devising methods for meeting the problems which arise in its treatment. Even the more serious types of the disease, those which were entirely beyond hope but a short time ago, are now being successfully treated. That we are able to relieve patients suffering from far-advanced lesions must not blind us to the most important fact that has been brought out by a quarter century of experience in the intensive treatment of tuberculosis, *viz.*, that early lesions are the most easily cured, and that they leave the patient in the most satisfactory state of health and most capable of carrying on his life's work. My experience leads me to state that it is practical rather than Utopian to believe that operative measures are only justifiable until such time as we are able to make early diagnoses and institute adequate treatment as soon as diagnoses are made.

In order to appreciate what each individual measure contributes to cure, it is necessary to have a fairly accurate understanding of the fact that tuberculosis is a bacteriologic disease which produces pathologic and immunologic responses which in turn alter anatomic structures and physiologic reactions. Some of these changes in structure and function are favorable while others are unfavorable. It is the duty of the physician, as far as he can, to recognize and promote the former and to prevent the latter.

Cure of Tuberculosis—An Immunity Reaction. The important factor in the cure of all infectious diseases is immunity. This is particularly evident in diseases of short duration, such as diphtheria and tetanus, in which the toxins are the lethal agents and the immunity is all but absolute; for these can be cured by the administration of immune bodies artificially produced. It is also readily understood in such diseases as typhoid in which protective inoculation of killed bacteria will immunize, or smallpox, in which an artificial vaccination will produce a miniature disease and protect the host from future disease. In tuberculosis, on the other hand, we have a disease, chronic in nature, which produces an immunity,

but one more difficult to understand. A miniature disease caused by a small number of bacilli will produce, at least for a time, a relative immunity against future inoculations, but is not able to grant a full immunity. Protection may also be granted by dead bacilli similar to that produced in typhoid vaccination, but again only relative and not so high as that given by a real infection caused by living bacilli.

Bacilli and the toxic substances produced by them are responsible both for the production of a relative increase in resistance to further inoculations and for injury and destruction of tissues. We have experimental evidence showing that inoculation of both living and dead bacilli will produce a relative degree of protection against new infection, and we have clinical observations which prove that the protective mechanism which is set going by natural inoculations of bacilli and bacillary products is effective in lessening the seriousness of later inoculations and in healing the disease.

In the natural healing of tuberculosis we rely on the patient's own body reactions to bring about healing, the same as in all other infectious diseases for which we do not have specific remedies. This protective mechanism differs with different individuals, both as to its efficiency and as to the time required for its development; but it is slow in all cases. This fact furnishes one of the chief causes of failure.

Tuberculous patients do not die because the disease is incurable, but because it is not cured. There is a time when nearly every patient suffering from tuberculosis has it within his power to attain a cure. That he does not do so is due to the fact that for one or another reason the disease is not brought under treatment at this favorable time, or that the kind of treatment is not suited to the condition at hand; or is not properly applied. We assume that healing is primarily a physiologic process, and that its accomplishment depends upon the establishment of a much higher degree of immunity than was necessary successfully to overcome the minor lesions of early infection.

We cannot describe categorically the factors which make for immunity, nor can we assign to each its particular part in bringing about healing, but we have learned that a good physiologic balance is a great asset. We have learned that rest is the most important single factor in maintaining such a balance during the stage of active disease. It produces its favorable effects in many ways. It lessens the energy requirements of the body at a time when the demands of increased energy cannot be easily supplied. It calls for a minimum of circulatory activity in the body and so in the lungs, and calls for a minimum of respiratory effort, thus putting the diseased areas at relative rest. This reduces the danger of metastases occurring and minimizes the escape of toxins from the foci, thus relieving

the patient of avoidable toxic symptoms. It reduces the body's food requirements to a minimum and permits of storing of any excess of energy for supplying future demands.

Rest of mind is as essential as rest of the body, so the development of a proper mental attitude is important. It can thus be seen that the control of the patient is necessary to guarantee to him a physical and mental rest. No matter what other measures are used in treatment, mental and physical rest should be maintained during the period when the disease is active.

If a carefully devised program, suited to the patient's particular requirements, is carried out sufficiently long, it will assure success in nearly all of those cases in which healing depends alone upon the resistance of the patient. In other words, a well-balanced physiologic state is sufficient to produce the cure in nearly every case at this favorable time.

I wish to emphasize this fact, because in our enthusiasm for operative methods we are prone to forget that if the disease were treated early, the conditions which require operation would be rarely met. Our slogan should be "early diagnosis and immediate, adequate treatment." In what instances are non-operative measures insufficient? This is the question to be considered.

The clinician may have his faith in the ability of the patient to cure his own disease greatly increased by patiently treating those who seem to offer little hope of cure unless the lung may be compressed by pneumothorax, or the tissues be relaxed by phrenic evulsion, and in whom attempts at the former have been unavailing and the institution of the latter has failed to cause elevation of the diaphragm, or by patiently treating certain extensive bilateral lesions which are not suitable for operation. In such cases it is not a rare thing to see the usual sanatorium regimen followed by healing.

I have formed the opinion from treating several thousand patients suffering from advanced and far-advanced tuberculosis that, if non-operative treatment is followed with sufficient detail and continued sufficiently long, most patients in whom we can establish and maintain a resistance sufficiently high to prevent extensive caseation with necrosis and serious new metastases from forming have an excellent chance of ultimately bringing their disease to a state of quiescence, and that, unless cavities which are too large or cavities possessed of dense walls, or mechanical conditions which prevent adequate compensation from taking place are present, they may go on to an eventual healing. It is the patients in whom metastases continue to take place, in whom destructive lesions are uncontrolled, or in whom mechanical factors interfere, that cannot heal readily.

The Mechanical Factors Which Interfere With Healing. As the disease progresses, however, there are certain factors which enter

into the picture that make healing difficult, sometimes even impossible, no matter how high resistance may be raised. These factors are largely of a mechanical nature.

The therapeutics of tuberculosis cannot be understood without taking these mechanical problems into consideration, for they really are the most important factors in separating tuberculosis into operative and non-operative. Too often, to the therapist, the cure of tuberculosis means some one particular thing—a hygienic regimen with rest and control as the chief factors, tuberculin, heliotherapy, pneumothorax, a phrenic evulsion or a thoracoplasty. Such an attitude toward cure is not rational and does not take into consideration the best conception of tuberculosis or the best interests of the patient.

The lungs are confined within the thoracic cage and are in close contact with rigid bony structures on all sides except at the base, where they are confined by the diaphragm. In tuberculosis a shrinking of the pulmonary volume takes place, whether as a result of destruction of tissue or by the replacement of elastic tissue by fibrosis, or by the reduction of the volume by exudation and atelectasis.

On the principle that Nature abhors a vacuum, the total volume of pulmonary tissue always must approach the amount necessary to fill the thoracic cage. When the volume of pulmonary tissue is reduced it can be compensated in only one of two ways: the structures which confine the lungs must contract and make the thoracic cage smaller, or the lungs themselves must compensatorily enlarge. These two processes go hand in hand as tuberculosis advances.

During the early stages of the disease the reduction in lung volume is of comparatively slight importance and usually is readily compensated by an emphysema of the uninvolved or less involved lung tissue. Later, too, it may be compensated, but with greater difficulty, and, finally, not at all. As soon as the stage is reached in which compensation is not readily made, healing is interfered with, and no matter how stable the patient's physiologic equilibrium or how competent his immunity, healing can go forward only with difficulty.

The mechanical conditions which particularly interfere with compensation are pleural adhesions, fixation of the mediastinum, adhesions and fixation of the diaphragm, widespread fibrosis, the emphysema which has developed prior to the time of the destructive lesion and rigid thorax.

The manner in which pleural adhesions interfere with healing may be studied in cases of bilateral apical tuberculosis, in which an apical, pleural cap is found on both sides. The tissues are rigidly fixed in an area as extensive as the adhesions. Contraction of the pulmonary tissues which accompanies the disease makes traction on the unyielding pleural adhesions. Since they cannot give way,

whatever compensating change occurs must take place from below, and, since the diaphragm is a muscle with strong contracting power, the compensation really must occur largely by the enlargement of the air cells, causing an emphysematous condition in that portion of the pulmonary tissue which is not involved in the tuberculosis. The seriousness of the interference which is caused by adhesions in double apical tuberculosis must be evident to any one who will note the extent of the shifting of the upper mediastinum which is at times necessary in order to compensate for the contraction which follows healing of unilateral lesions which involve the upper portion of the lung. The tension to which these tissues would be subjected were the mediastinum fixed is evident.

Again, the interference with healing which is caused by pleural adhesions is shown when an extensive one-sided adhesive pleuritis exists over a lung which is the seat of a severe lesion of either the exudative or the proliferative type. If a fixed mediastinum is also present, healing may take place, but is rendered very difficult without some operative measure which will aid in adjusting the intrathoracic space to the lung volume. If the adhesions do not involve the entire pleura, a partial pneumothorax may be of value, or a phrenicectomy may afford a considerable degree of aid. If a cavity of any considerable size is present, and particularly if it is situated in the midst of fibrous tissue and possessed of a thick wall, healing is rendered very doubtful, except as a result of operative assistance. Under these circumstances thoracoplasty may become practically our only hope.

The Characteristics of Proliferative and Exudative Lesions Which Modify Treatment. While the curability of tuberculosis depends upon the extent, age and activity of the lesion, it again depends upon whether it is predominantly proliferative or predominantly exudative. That there is a difference in exudative and proliferative tuberculosis has long been known, and recently we have begun to understand certain of the fundamental causes of this difference. The fact of this difference must be considered in applying therapeutic measures.

Predominantly proliferative tuberculosis has long been recognized as a comparatively benign process, one which primarily makes for fibrosis with chronicity rather than for acuteness with destruction. It has long been assumed that it is caused by relatively few and mildly virulent bacilli, and that the predominant reaction of the tissues is that of cellular proliferation rather than exudation and destruction.

Now that pure fractions of the bacillus have been given to us with which to work, it has been found experimentally that bacillary lipoids produce fixed-cell proliferation and tubercle formation, with little toxemia or exudative reaction, while bacillary protein causes exudation and destruction, and the polysaccharid seems to be the

chief toxic element. Sabin, using a phospholipin and injecting it into the peritoneal cavity of animals, has been able to produce huge proliferative masses of tissue, so we now explain proliferative tuberculosis as being predominantly a reaction of the body to the lipoids of the bacillus, to the bacillus as a foreign body, in contradistinction to its reaction to the bacillary proteins and polysaccharids or the bacillus as a living immunizing substance.

It is also characteristic of predominantly proliferative tuberculosis that it extends in spite of its mildness. It seems to fail in calling out the immunizing mechanism which raises the patient's specific resistance, prevents the ready passage of bacilli through the tissues and increases the body's power to destroy them. Sooner or later, however, exudative phenomena appear, destruction of tissue takes place, symptoms of intoxication supervene and the process becomes a combination of proliferative, exudative and often destructive characteristics with increased acuteness, and, at the same time, with evidence of a heightened immunity. Unfortunately the immunity makes its appearance, as a rule, after extensive fibrosis has taken place, and the tissues are harboring widespread infection.

Predominantly proliferative tuberculosis, because of its mild nature, bears a reputation for ready healing which it does not deserve. In my experience a proliferative lesion produces milder reactions, extends more slowly, but often is far more difficult to heal than a preponderantly exudative lesion of similar extent. And when it does heal it leaves the lung tissue replaced by extensive scar, while the exudative lesion heals largely by resolution, leaving only a minimum amount of scar.

Predominantly exudative tuberculosis is a more acute process. We assume that it is caused by larger quantities of more virulent bacilli than those which are responsible for the preponderantly proliferative lesions, and that through their growth, rapid multiplication and destruction, large quantities of bacillary lipoids, protein and polysaccharids are set free in the tissues. The exudative response is called out as the body's reaction to the protein fraction, which is the same fraction that stimulates the patient's immunity mechanism. The toxicity, however, is probably largely due to the polysaccharid. New tissue formation takes place as a healing measure, but it is limited in extent and secondary to resolution of the exudate. Extensions do not take place gradually, as in the predominantly proliferative type of disease, but more precipitately and result in more acute reactions on the part of the patient, a greater toxicity and a more efficient immunity.

The symptoms of acuteness result from the rapid destruction of bacilli and the liberation of bacillary products, particularly the polysaccharids and proteins.

Pulmonary Lesions Which May Heal By the Hygienic Rest Regimen Alone and Those Which Require Operative Assistance. From the purely scientific standpoint in which the curability of tuberculosis

alone is considered, the following types will heal fairly regularly without operative assistance:

1. Early limited lesions of either the proliferative or exudative type.
 2. Proliferative lesions more extensive than those mentioned under Group 1, involving one or both lungs, provided they have not taken on extensive metastases and destructive processes with multiple cavitation.
 - (a) Small cavities may usually be expected to heal, but the healing of large ones, especially if multiple, is more doubtful without operative aid.
 - (b) Whether or not such lesions will heal depends much upon the extent of injury which has been done to the lung tissue and the ease with which the necessary compensatory changes between lung volume and intrathoracic space may be made.
 3. Exudative lesions more extensive than those mentioned in Group 1, with or without cavity, provided the non-infected lung tissue can take on the required emphysematous changes and the mediastinum is free to shift in case it is required by the compensation which must be made, and provided further that other limiting structures are able to accommodate themselves to the reduced lung volume.
- Early cavity in exudative tuberculosis is not a contraindication to healing unless it is held open by pleural adhesions and a fixed mediastinum, or so located that it cannot close.
4. Exudative lesions which are accompanied by extensive atelectasis will usually heal even though they may be accompanied by high temperature which requires several months to reach normal.

From the purely scientific standpoint, this leaves practically no early cases that regularly require operative assistance, but as the disease advances there are several types of lesion which cannot be depended upon to heal without operative aid, some of which are the following:

5. Comparatively small lesions with a cavity which is held open by pleural adhesions, and is prevented from closing because the unaffected lung tissue is not able to make the necessary compensatory changes, such as apical or subapical cavities covered by a pleural cap, and especially when the upper mediastinum is fixed.
6. Any active lesion which continues to form metastases unduly long in spite of carefully followed non-operative treatment.
7. Lesions in which a destructive process is seriously threatening cavity formation; in fact, should cavitation threaten during the course of chronic tuberculosis, it should probably always be prevented by collapse if possible.
8. Any lesion which is prevented from healing by mechanical hindrances. This will include:
 - (a) Small cavities situated so that the walls cannot collapse as in the apex covered by a pleural cap; small cavities in dense scar tissue situated in any part of the lung; and those near the hilum or diaphragm.
 - (b) Extensive infiltration, with or without cavity, in which the tissues are put on marked tension, and in which compensation necessary to healing cannot be readily made.
 - (c) Large cavities with thick fibrous walls.
 - (d) Cavities in a much contracted lung, with displaced mediastinum, in which further compensation cannot be made.

In my experience this grouping roughly separates the cases which may be expected to heal by non-operative measures from those which require operative assistance. It does not, however, repre-

sent the manner in which tuberculous patients are generally treated, because operative measures are so frequently found necessary to meet the exigencies under which treatment is carried out. Not only are the Groups 5, 6, 7 and 8 recognized as requiring operative aid, but some of Group 1, many of Groups 2 and 3 and practically all of Group 4 are usually treated by pneumothorax or phrenicectomy or both.

TUBERCULOSIS CASE-FINDING.

FIVE YEARS' EXPERIENCE WITH FLUOROSCOPY.

By ADA CHREE REID, M.D.,

ATTENDING PHYSICIAN, NEW YORK INFIRMARY; ASSISTANT PHYSICIAN, OUT-PATIENT DEPARTMENT, NEW YORK HOSPITAL, NEW YORK, N. Y.

(From the Medical Division of the Metropolitan Life Insurance Company.)

It has been shown definitely and frequently that pulmonary tuberculosis exists in many cases without abnormal physical signs and without suggestive symptoms. Therefore, in this discussion it will be taken for granted that, at the present time, the most effective and most secure way of making an early and definite diagnosis is by the use of the stereoscopic Roentgen ray film. This is the ideal method and the more frequently and repeatedly it is utilized, the more effective it becomes. It has, however, the disadvantage of expense, which, in many instances, is a decided drawback. Certainly this is apt to be true where large numbers of supposedly healthy people are to be examined; routine roentgenograms may be so expensive as to be prohibitive. If all, then, cannot be Roentgen rayed, the question arises how to select those cases which should have a Roentgen ray. Some or all of the following may be used as a basis for selection: (1) Physical examination; (2) history of suggestive symptoms or of contact with tuberculosis; (3) tuberculin reaction; (4) paper films; (5) fluoroscopic examinations.

The first method (physical examination) can be dismissed as being grossly inaccurate as a selective measure. This has been pointed out repeatedly.^{1-8, 15} We do not wish to imply that physical examination of the chest should be omitted, but we emphasize that a negative physical examination does not rule out the presence of tuberculosis. On the other hand, the only reliable physical sign is the presence of râles persisting after cough, usually in the upper part of the chest. If these are present, the diagnosis of tuberculosis is to be strongly considered; if they are absent, tuberculosis may still be present in advanced degree. Other signs—cogwheel breathing, slight variations in percussion note and in intensity of breath sounds—are solely of academic interest; they have no practical value in establishing the diagnosis of tuberculosis.

The second method (history-taking) is of great assistance. All cases with a history of pleurisy, hemoptysis or cough of unusual duration should be Roentgen rayed. However, there are innumerable cases of early tuberculosis which do not present characteristic symptoms, but rather vague, ill-defined complaints (as lassitude, irritability, abdominal discomfort, menstrual variations, etc.), none of which seem related to disease of the respiratory system. Insistence that such a patient have a Roentgen ray of his chest is wise, but it is often difficult to accomplish. Moreover, there are many individuals with early (or advanced) tuberculosis in whom symptoms of any sort are either entirely absent or so slight that they escape attention^{9,10}—the “Tuberculosis Unappercepta” of the German writers. “It is probable that every actual case of tuberculosis is preceded by such a phase, during which the fate of the patient is already, in many cases, decided to his disadvantage, unless his infection be discovered early through Roentgen ray examination.”¹¹

We have, for five years, observed a group similar to this (*i. e.*, positive Roentgen ray findings—absence of physical signs and symptoms) and have seen the disease progress in some instances to cavitation with an absence of signs and symptoms.¹² In our experience, early cases with no definite signs or characteristic symptoms far outnumber those cases presenting suggestive symptoms. We feel, therefore, that a selection for Roentgen ray based on symptoms will fail to include a large number of clinically significant cases.

The remaining case-finding methods are based upon laboratory procedures. The tuberculin reaction is of considerable value, more particularly in schoolchildren. As a basis of selection among adults, it is of less value because the number of positive reactors is so high.

The paper films, recently introduced as an economic method of examining large groups quickly, may prove to be a satisfactory screen for further Roentgen ray when large numbers of individuals can be examined in rapid succession. It is certainly superior to physical examination and has the advantage of being a record which can be reviewed or filed for further study. However, it shares with the celluloid film the disadvantage of requiring expensive apparatus, additional personnel, space, etc.—the items which determine the cost of a Roentgen ray film. In our own case the saving produced by using paper films would be too slight to offset the disadvantage that they do not produce roentgenograms of the same clearness as do celluloid films.

The basis of selection for Roentgen ray examination used at our Home Office in its medical examination of applicants for employment is fluoroscopy. After a careful history-taking (in which the patient may willfully or unconsciously conceal important facts) and after a routine physical examination, each applicant is fluoro-

scoped by the examining physician following a prescribed technique. Every suspicious or positive case is referred for Roentgen ray films. Before analyzing our results, we would like to point out some of the advantages of the fluoroscopic examination *per se*.

1. It has special diagnostic value in determining the mobility of the diaphragm and the range of expansion of the lungs. We recall a case of very early tuberculosis barely perceptible on the Roentgen ray films which was noted on the fluoroscopic examination because of the easily apparent splinting of the ribs over the lesion.

2. During the fluoroscopic examination, it is possible to observe the chest from many angles and thus to view the areas close to the heart and mediastinum which are difficult to record in the film. Occasionally a small lesion can be detected by fluoroscopy while rotating the patient, since the rays strike the lesion at the most advantageous angle. The patient can be viewed in the antero-posterior as well as in the posteroanterior diameter. By way of illustration, we have seen a cavity, 1 cm. in diameter, picked up on fluoroscopic examination in the posteroanterior position which was visible on only 1 of a pair of stereoscopic films. It is possible for a serious infiltration to be concealed by the clavicle and ribs in 1 film, but visible on the other of a stereoscopic pair. Furthermore, during a fluoroscopic examination, the chest may be viewed with scapulæ rotated out of the lung fields; the clavicles may be elevated or lowered; thick neck muscles may be pushed aside in order to view the infraclavicular regions and posterolateral 3d and 4th interspaces, where many of the rapidly progressive tuberculous infiltrations of early adult life begin. In our experience the fluoroscopic examination carefully performed will miss very few cases.

From an administrative point of view, fluoroscopy has many definite advantages: (1) The equipment is relatively inexpensive and the upkeep low. (2) The technique of fluoroscopic examination is readily acquired. Our fluoroscopic examinations are made by our examining physicians, who, after a short training period perform the examinations effectively (the majority have had no previous fluoroscopic experience). (3) The decision regarding the examination is immediate and there is no delay. We believe that the fluoroscopic examination is a cheaper method than the taking of a single flat film, is more rapid and is approximately as accurate.

We have determined our percentage of error by routinely comparing the fluoroscopic findings on a group of persons with the Roentgen ray reading. At their annual examination, chest Roentgen ray and fluoroscopic examinations have been made of 1035 employees who had not been under observation and were supposedly healthy. Among the 1035 were 47 cases which showed some abnormality, such as a cervical rib, azygos lobe, diaphragmatic pleurisy, tuberculosis, enlarged heart or aorta, foreign body, etc. We found that in 1035 examinations only 2 cases of tuberculosis of clinical

significance were missed on the fluoroscopic examination and these were very minimal cases. On the other hand, we find the fluoroscopists describing and naming abnormalities, such as the azygos lobe, accurately 6 times out of 7. We are satisfied that our percentage of error is very small.

In the campaign against tuberculosis in the German universities, fluoroscopy is considered to be a very important, if not the most important, part of the examination. In fact, since the summer semester of 1930, the fluoroscopic examination has been obligatory at the University of Munich. Doctor Kattentidt, in charge of Student Health at Munich, states: "It was experienced everywhere that the preceding clinical examination detected only a small fraction of the tuberculosis cases which were found by the fluoroscopic examination;" and further: "Dr. V. Romberg proved that 95% of all the cases detected by Roentgen ray pictures can also be diagnosed by fluoroscopic examination."¹³

In Lemberg, Poland, fluoroscopy of all newly matriculated students of all 5 colleges was introduced in 1930 and has been continued since. The method is being adopted rapidly by other universities: Münster, in Westphalia; Lund, Sweden; Heidelberg, etc.

Doctor Braeuning makes a statement with which we are in complete accord, *i. e.*, "Every department should have its own fluoroscope, and this examination should be made by the department staff and not by the central Roentgen ray department."¹¹

We believe, in analyzing our experience* with fluoroscopy since 1927, that it has been a very valuable procedure. Prior to October 1, 1927, applicants for employment received a complete physical examination routinely and were Roentgen rayed only if suspicious symptoms or signs were elicited at this examination; each year several employees who had been in service less than 1 year developed active tuberculosis (in 1927, with an average clerical payroll of 9582, there were added 3094 employees; in the same year there were 11 cases of pulmonary tuberculosis among employees of less than 1 year's service, *i. e.*, 35.5 new cases per 10,000 new employees). After the fluoroscopic examination was introduced, we consistently discovered each year by this method 1% of tuberculosis among our applicants for employment (Table 1) and the number of new cases in employees of less than 1 year of service has decreased materially. (In 1932, with an average clerical payroll of 11,814 and 1707 new employees, there was only 1 case of tuberculosis among employees of less than 1 year's service, *i. e.*, 5.8 per 10,000 new employees.)

The fluoroscope has detected, therefore, those cases of tuberculosis among applicants who, in the past, had escaped detection at their preemployment examination and who became, many of them, cases of active tuberculosis within the first year of employment.

* Approximately 17,000 fluoroscopic examinations are made each year by physicians in the Medical Department of our Home Office.

TABLE 1.—INCIDENCE OF TUBERCULOSIS AMONG APPLICANTS FOR EMPLOYMENT.

Year.	Number of applicants.	Cases of tuberculosis.*					
		Total.	Detected by			Incidence of Tbc. per 1,000.	Detected only through fluoroscopy (per cent).
			History.	Physical signs.†	Fluorosc.†		
1928	4405	69	9	7	50	15.6	76
1929	4780	57	6	6	45	11.6	79
1930	3105	36	3	1	32	11.2	91
1931	2175	33	2	4	27	12.44	82
1932	2134	32	2	0	30	14.0	96

* In addition, the following chest conditions other than tuberculosis escaped physical examination but were detected with the fluoroscope; thymoma; substernal thyroid, 2; esophageal pouch, 1; enlarged aorta, 2; enlarged heart, 1; calcified pleura, 1; adhesive pleurisy, 4.

† The physical examination is checked, if there are abnormal fluoroscopic findings. However, the number of corrections is surprisingly low, even though the examiner knows the area in which the lesion is located.

The incidence of new cases of tuberculosis among our employees has also been reduced (Table 2):

TABLE 2.—INCIDENCE OF NEW CASES OF TUBERCULOSIS* AMONG H. O. EMPLOYEES.

Year.	H. O. Employees.	New cases of Tbc.	Cases per 10,000.
1928	11,530	106	92
1929	11,966	85	71
1930	12,468	71	71
1931	13,081	72	57
1932	13,582	59	43

* Including active, questionably active and apparently healed.

An even greater result has been accomplished in respect to the early diagnosis of tuberculosis. Using the fluoroscope freely at annual examinations and in the medical rest rooms, we have been able to detect tuberculosis in its early stages, so that the cases admitted to our Sanatorium in 1932 were 76% incipient and 24% advanced, while in 1928, 47% were incipient and 53% advanced.

Fluoroscopy has been subjected to criticism as to its accuracy because of the fact that active tuberculosis has developed among young adults who apparently had a negative fluoroscopic examination a short time previously, the conclusion being that the fluoroscope failed to reveal definite disease which must have been present. This is not necessarily true. We have seen many who have developed definite Roentgen ray evidence of tuberculosis after a negative film of the chest, some within 3 months of the negative film.

Dr. Braeuning reports 19 cases of tuberculosis under his observation which had developed between 2½ to 12 months after a negative Roentgen ray;¹¹ Dr. Rist, of the Laennec Hospital in Paris, states he

has had apparently normal Roentgen rays of lungs a few days previous to the onset of extended tuberculosis.¹⁴

Summary. The most reliable method of detecting pulmonary tuberculosis is by means of the Roentgen ray film, but as a routine procedure in examining large numbers of supposedly healthy individuals, it has the disadvantage of being expensive. We have discussed the various methods available for selecting those cases which shall have films made.

Physical examination of the chest fails to detect many, especially early, cases of pulmonary tuberculosis.

A case-finding method based upon history is also inadequate, since tuberculosis may be present to an advanced degree without significant symptoms.

The tuberculin test is of considerable value in selecting those cases of childhood tuberculosis which shall have Roentgen ray films, but its application to adults is less satisfactory because of the large percentage of reactors.

Paper films at their present stage of development do not produce roentgenograms of the same clearness as celluloid; the cost of the finished product is only slightly less than that of the celluloid.

Fluoroscopy as a method of examination has many advantages which have been described. Moreover, it is inexpensive and the technique easily acquired. Its accuracy has been demonstrated by determining our percentage of error in 1035 cases first fluoroscoped, then filmed, and finding it very low. Its practical value to us has been proved by an analysis of our tuberculosis statistics during the 5 years this method has been used. These statistics show that: (1) We have detected each year among applicants for employment 1% of tuberculosis which would otherwise have escaped discovery; (2) we have reduced our incidence of new cases of tuberculosis from 92 per 10,000 in 1928 to 43 per 10,000 in 1932; (3) we are detecting tuberculosis in the early stages; sanatorium admissions in 1928 were 47% minimal; in 1932, 76% minimal.

Conclusion. The Roentgen ray film examination of the chest is the most reliable method available for detecting pulmonary tuberculosis. Fluoroscopy, by reason of its accuracy, economy, rapidity and simplicity of technique, is the most efficient basis of selection for complete roentgenographic examination.

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THE RELATIONSHIP OF THE INTRINSIC FACTOR TO A HEMATOPOIETIC MATERIAL IN CONCENTRATED HUMAN GASTRIC JUICE.

BY O. M. HELMER, PH.D.,

PAUL J. FOUTS, M.D.,

AND

L. G. ZERFAS, M.D.,

INDIANAPOLIS, IND.

(From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, and the
Department of Medicine, Indiana University School of Medicine.)

It has been shown¹ that the incubation of 100 cc. of normal gastric juice with 1 vial of Liver Extract No. 343 markedly increases the potency of the liver extract. This increase in potency is probably the result of the interaction of the intrinsic factor of the gastric juice upon an extrinsic factor in the liver extract. Because of the uniformity of the product and its small bulk, the liver extract would seem to be a better source of the extrinsic factor than beef muscle in testing for the presence of the intrinsic factor. In previous studies² it has been shown that before a hematopoietically stimulating material can be demonstrated in normal human gastric juice by the intramuscular injection into patients having pernicious anemia, some change in the gastric juice must take place. This change can take place during the concentration by vacuum distillation or during the storage of the gastric juice in the ice box for 2 months.

It is the purpose of this paper to report studies on the relationship of the intrinsic factor to the hematopoietic material in concentrated human gastric juice and attempts to determine some of the characteristics of the intrinsic factor.

Methods. The patients used in these studies were all typical clinically and hematologically of pernicious anemia. Daily red blood cell counts, hemoglobin determinations (Newcomer) and reticulocyte counts were made during the control and test periods. One vial of Liver Extract No. 343 was incubated for 4 hr. at 40° C. with the gastric juice, or the fraction of gastric juice, to be tested, as described previously.¹ These liver extract gastric juice digests were brought to pH 5 just previous to administration to the patients. During the test periods the patients received meat-free,

low vitamin B₂ diets. The patients received the noon meal at 11 A.M. and then received no food until 6.30 P.M. At 4.30 P.M. the gastric juice liver extract digests were administered. All the patients received the test materials daily for 10 days. The patients who had slight or no responses from the test materials responded to known potent materials administered by mouth before the experiments were considered negative.

The ultrafilters used were of the Bechold type described previously.² When the gastric juice was concentrated by vacuum distillation, the same procedure as in the preceding paper² was carried out. When the pepsin and rennin were adsorbed on casein, a method similar to that described by Hammarsten³ was used. A 7.5% solution of Hammarsten casein in 4% sodium carbonate was added to a known quantity of gastric juice until a pH of 4.7 to 5 was obtained, which is the point of maximum precipitation. The casein precipitate was removed by centrifugalization and filtration. The filtrate is water-clear and filters rapidly. By the methods employed, no pepsin and only insignificant amounts of rennin could be detected in the filtrate. When the casein precipitate was used in the experiments, it was washed by stirring the precipitate with a buffer at pH 4.7, centrifuging and decanting the wash fluid.

Results. I. *The Effect of the Incubation of Varying Amounts of Normal Human Gastric Juice upon the Potency of Liver Extract.* In Table 1 are recorded the responses of the red blood cells, hemoglobin, and reticulocytes to the daily administration of 1 vial of liver extract that had been incubated with 10, 25 and 50 cc. of normal human gastric juice and to the subsequent administration of Extralin. The responses of the reticulocytes of Case 1 to the liver extract incubated with 10 and 25 cc. were distinctly not maximal (9.6% and 8.1% at red blood cell levels of 1.55 and 2.02 million). There was only slight clinical improvement and no sustained rise in red blood cells. There was a good clinical and hematologic response after the patient received Extralin, capsules 4 t. i. d., a. c. There was a good clinical improvement when Case 2 received daily 1 vial of liver extract which had been incubated with 50 cc. of gastric juice. The reticulocytes reached 17.2% on the 9th day when the red blood cell count was 2 million, and there was only a slight rise (3.4%) following the subsequent administration of Extralin.

These studies would indicate that 10 and 25 cc. of normal human gastric juice did not contain sufficient intrinsic factor to react with 1 vial of liver extract to produce a maximal reticulocytosis. However, it is interesting that as little as 10 cc. increases the potency of liver extract enough to cause a slight reticulocytosis. Fifty cc. seems to be near the minimal amount of gastric juice necessary to combine with 1 vial of liver extract. These findings indicate that there must be some quantitative relationship between the amounts of intrinsic and extrinsic factors present to produce maximal reticulocyte responses. Castle and his associates⁴ demonstrated that 75 cc. of the juice is sufficient to interact with 200 gm. of beef muscle. Therefore, somewhere between 50 and 75 cc. should be the minimal amount necessary to combine with 1 vial of liver extract to produce a maximal reticulocytosis.

TABLE 1.—THE RESPONSE OF THE BLOOD TO THE DAILY ADMINISTRATION OF ONE VIAL OF LIVER EXTRACT NO. 343 INCUBATED WITH 10, 25, AND 50 CC. OF NORMAL HUMAN GASTRIC JUICE.

Case number	1	1	2			
Age	62	62	39			
No. cc. G. J. incubated with 1 vial of L. E. No. 343	10	25	50			
Days.	R. B. C. per cmm. in millions.	Hgb. %* Ret. %	R. B. C. per cmm. in millions.	Hgb. %* Ret. %	R. B. C. per cmm. in millions.	Hgb. %* Ret. %
0	1.65	31 0.1	1.46	30 5.2	1.44	34 1.0
1	1.73	31 0.6	1.55	35 4.5	1.44	34 0.8
2	1.43	35 0.6	2.02	34 6.1	1.72	32 0.6
3	1.58	31 0.6	2.02	34 8.1	1.67	32 0.4
4	1.34	26 1.0	1.61	39 3.5	1.53	32 0.8
5	1.25	27 2.6	1.53	39 2.3	1.79	37 2.8
6	1.44	30 4.8	1.46	40 4.4	1.50	30 6.9
7	1.55	31 9.6	1.52	42 5.1	1.94	33 14.6
8	1.48	31 5.3	1.56	42 2.6	1.94	33 17.4
9	1.46	30 5.2	1.70	42 5.7	2.00	32 17.2
10	1.46	30 5.2	1.70	42 8.4	1.93	38 15.6
11	1.46	30 5.2	1.70	42 8.4	2.15	41 14.1
12	1.46	30 5.2	1.70	42 8.4	2.31	38 10.1
13	1.46	30 5.2	1.70	42 8.4	2.31	38 10.1
14	1.46	30 5.2	1.70	42 8.4	2.51	42 12.8
15	1.46	30 5.2	1.70	42 8.4	2.40	44 11.6
16	1.46	30 5.2	1.70	42 8.4	2.37	47 7.7
17	1.46	30 5.2	1.70	42 8.4	2.38	47 5.0
18	1.46	30 5.2	1.70	42 8.4	2.84	50 4.3
Subsequent medication			Extralin, caps. 4 t. i. d.		Extralin, caps. 4 t. i. d.	
0	1.70	42 8.4	2.84	50 4.3	2.84	50 4.3
1	1.81	42 8.0	2.54	44 2.5	2.54	44 2.5
2	2.02	44 6.3	2.63	47 1.8	2.63	47 1.8
3	1.94	47 6.9	2.44	50 1.5	2.44	50 1.5
4	2.18	50 12.7	2.48	55 1.8	2.48	55 1.8
5	2.17	49 11.9	2.91	55 3.0	2.91	55 3.0
6	1.83	53 7.7	2.98	50 3.4	2.98	50 3.4
7	1.98	52 5.5				
8	2.25	58 7.6				
9						

* Newcomer method.

II. *The Effect of Gastric Juice Concentrated by Ultrafiltration and the Ultrafiltrate of Normal Gastric Juice upon the Potency of 1 Vial of Liver Extract.* Case 3 first received for 10 days 1 vial of liver extract that had been incubated with 150 cc. of the portion of the normal human gastric juice which passed through the ultrafilters (ultrafiltrate). The concentration of pepsin in the original gastric juice averaged 4.2 mg. and rennin 42 mg. per cc. The ultrafiltrate contained 0.1 mg. of pepsin and 1 mg. of rennin per cc. Chart I shows that there was a slight reticulocyte rise (3.4%) following this medication; however, there was no clinical improvement. The patient then responded to 1 vial of liver extract that had been incubated with the portion of this gastric juice which was held back by the ultrafilters (concentrate). The reticulocytes reached 10.1% on the 7th day, when the red blood cell count was 3.01 million. There was satisfactory clinical improvement and a good rise in red blood cells and hemoglobin, as is shown in Chart I.

These studies showed that almost all of the intrinsic factor had been held back by the ultrafilters. In the previous work it was shown that the portion of the gastric juice held back by the ultrafilters could be made hematopoietically active, as demonstrated by the intramuscular injection into patients having pernicious anemia, when concentrated by vacuum distillation, while the ultrafiltrate could not be made active by the same procedure. Therefore, from the above tests it can be assumed that the portion of the gastric juice which can be made active for intramuscular injection contains the intrinsic factor at the onset of the vacuum distillation and the portion which cannot be made active does not.

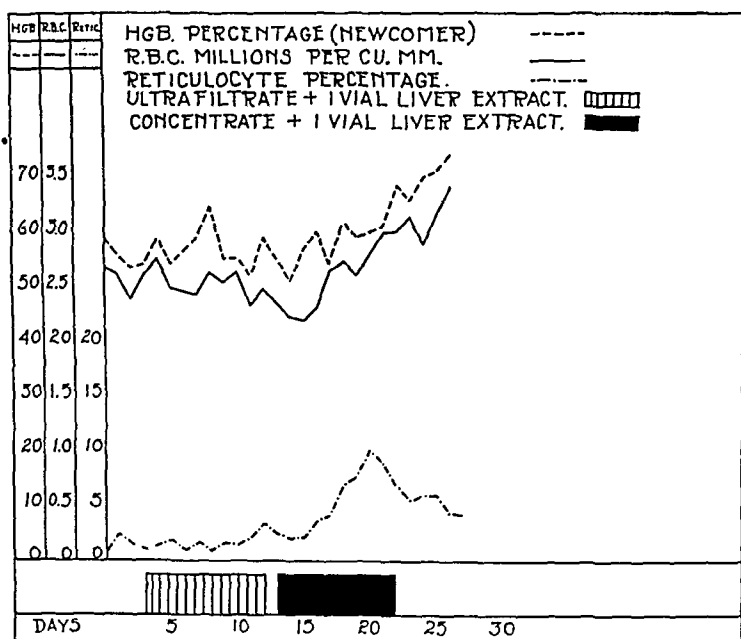


CHART I.—Response (Case 3) to the daily administration of 1 vial of Liver Extract No. 343 incubated with the ultrafiltrate of normal human gastric juice and to 1 vial of Liver Extract No. 343 incubated with the portion of the gastric juice concentrated by the ultrafilters.

III. *The Effect of the Incubation of Gastric Juice Concentrated by Vacuum Distillation and then Diluted with Water upon the Potency of Liver Extract.* Fresh human gastric juice (1200 cc., divided into 2 equal parts) was concentrated to 21 cc. by vacuum distillation and then diluted to 1000 cc. The concentration of pepsin in the original gastric juice averaged 4.4 mg. and rennin 49 mg. per cc. The gastric juice after concentration by vacuum distillation and dilution with water contained 1.3 mg. of pepsin and 9 mg. of rennin per cc. Of this material 100 cc. was incubated with 1 vial of liver extract and administered daily to Case 4. There was a slight reticulocytosis (8% on the 11th day when the red blood cell count was 2.21 million and the hemoglobin 48%), but there was little or no

clinical improvement. Table 2 shows the responses of the blood to this medication and to Extralin. This patient had a rather high reticulocyte count on entering the hospital; however, after a 7 days' control period the red blood cell count had dropped from 2.27 to 1.85 million, although the reticulocyte count was still 3%. A very good clinical response and reticulocytosis of 27% (red blood cell count 2.21 million) followed the administration of Extralin. There was also a good rise in red blood cells.

TABLE 2.—THE RESPONSES OF THE BLOOD OF PATIENTS HAVING PERNICIOUS ANEMIA TO THE DAILY ADMINISTRATION OF ONE VIAL OF LIVER EXTRACT No. 343 INCUBATED WITH NORMAL HUMAN GASTRIC JUICE CONCENTRATED BY VACUUM DISTILLATION AND THEN DILUTED.

Case number	4	5	5						
Age	46	66	66						
Enzymes in original G. J. (aver. mg. per cc.)	Pepsin 4.4 Rennin 49.0	Pepsin 2.9 Rennin 32.0	Pepsin 2.9 Rennin 32.0						
Enzymes in G. J. after vacuum distillation (aver. mg. per cc.)	Pepsin 1.3 Rennin 9.0	Pepsin 1.95 Rennin 22.0	Pepsin 1.95 Rennin 22.0						
Enzymes in ultrafiltrate (aver. mg. per cc.)	Rennin 0.8							
Material derived from No. cc. G. J. incubated with 1 vial of L. E. No. 343	120	120	120						
Days.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.
0	1.85	38	3.0	2.01	49	1.4	53	0.6
1	2.13	38	3.0	1.0	1.90	49	1.3
2	2.17	43	2.7	2.00	53	0.7	1.83	49	1.7
3	1.79	44	2.5	1.99	53	0.8	2.07	45	2.2
4	1.76	45	2.4	2.11	53	0.4	1.95	47	1.7
5	2.04	42	4.0	2.07	51	0.5	2.4
6	2.7	2.02	49	0.3	1.80	45	3.6
7	2.04	39	4.4	1.90	53	0.8	1.95	..	2.2
8	1.90	45	5.7	1.51	..	0.8	1.72	..	1.2
9	2.11	41	5.8	2.11	53	1.2	1.70	47	2.0
10	2.10	40	6.4	53	0.6	2.01	43	2.1
11	2.21	47	8.0	1.83	42	2.0
12	1.90	50	5.8	2.5
13	3.5	2.21	43	1.8
14	2.03	44	3.4						
15	1.97	45	2.0						
16	1.61	40	1.0						
Subsequent treatment	Extralin, caps. 4 t. i. d.			Extralin, caps. 4 t. i. d.					
0	1.61	40	1.0	2.21	43	1.8
1	2.15	42	2.8	1.80	44	1.6
2	1.59	44	4.0	1.66	43	2.8
3	1.79	38	4.9	1.93	42	2.0
4	9.8	1.83	43	11.2
5	1.85	40	25.6	1.86	43	12.8
6	2.21	..	27.0	14.8
7	2.17	47	22.4	23.8
8	2.83	41	23.6	1.93	43	21.8
9	3.25	54	12.6	2.50	47	15.2
10	2.65	54	17.0	2.94	55	13.2
11	12.4	2.36	54	8.8
12	3.18	53	11.7	2.72	59	9.0
13	2.88	50	13.3	2.61	59	9.6
14	2.96	61	4.0
15	3.09	62	

* Newcomer method.

Another 1200 cc. of fresh gastric juice (divided into 2 equal parts) was concentrated to 30 cc. by vacuum distillation and then diluted

to 1000 cc. The original gastric juice contained 2.9 mg. of pepsin and 32 mg. of rennin per cc. The gastric juice after concentration by vacuum distillation and dilution contained 1.95 mg. of pepsin and 22 mg. of rennin per cc. The gastric juice was then ultrafiltered. Of the ultrafiltrate 100 cc. was incubated with 1 vial of liver extract and administered daily to Case 5. As is shown in Table 2, there was no response of the blood or improvement in the clinical condition of the patient. The portion of the gastric juice held back by the ultrafilters was then diluted to 1000 cc. and 100 cc. of this was incubated with 1 vial of liver extract and administered daily to Case 5. This medication was followed by a rise in the reticulocytes up to 3.6% by the 6th day; but at the end of 13 days there was only slight change in the red blood cell level and no improvement in the condition of the patient. There was then a rise in reticulocytes up to 23.8% on the 7th day of Extralin therapy. There was a very satisfactory clinical improvement and rise in red blood cells and hemoglobin (Table 2).

It is evident from these findings that most of the intrinsic factor is either destroyed or used up during the process of concentration by vacuum distillation. The concentration by vacuum distillation, however, is necessary for the production of the material in the human gastric juice capable of stimulating the hematopoietic system of patients having pernicious anemia when injected intramuscularly. A goodly percentage of the pepsin and rennin in the gastric juice was likewise destroyed by the process of concentration by vacuum distillation.

The small amount of intrinsic factor remaining in the gastric juice concentrated by vacuum distillation was held back by the ultrafilters, while most of the material in the concentrated gastric juice which is active when injected passed through the filters.² It would therefore seem more evident that these two materials are not the same, although it has not been shown as yet that the intrinsic factor does not combine with some extrinsic factor during the concentration by vacuum distillation to form the material hematopoietically active when injected.

IV. *Studies on the Intrinsic Factor Freed from Pepsin and Rennin by Casein Precipitation.* In this group of studies the enzymes pepsin and rennin of the gastric juice were precipitated out on casein at pH 4.7 as described under "Methods."

Case 6 received daily for 10 days 1 vial of liver extract which had been incubated with the precipitate containing 3.7 mg. of pepsin and 33 mg. of rennin per cc. after the precipitate had been redissolved in 0.3% hydrochloric acid and brought up to the original volume of the gastric juice. Of this material 125 cc. was used daily. There was a rise in reticulocytes up to 5.6% (red count 1.77 million) on the 6th day, but there was no rise in red blood cells or improvement in the condition of the patient.

The amount of supernatant liquid (containing 0 mg. pepsin and

0.05 mg. rennin per cc.) equivalent to 125 cc. of the original gastric juice was incubated with 1 vial of liver extract and administered daily for 10 days to Case 7. Table 3 shows the marked reticulocyte rise (37.4% at a red blood cell level of 1.76 million) following this therapy. There was a very satisfactory improvement in the clinical condition and a rise in red blood cells. There was no subsequent rise in reticulocytes following 3 daily intramuscular injections of concentrated liver extract.

These tests showed conclusively that most of the intrinsic factor remained in the supernatant liquid, although the pepsin and rennin was completely precipitated out of the liquid. Castle and his associates⁵ in similar experiments, using beef muscle as the source of the extrinsic factor, reported that the intrinsic factor could be separated from the enzymes pepsin and rennin by casein precipitation.

Case 8 received 150 cc. of this supernatant liquid daily for 10 days to see if by the casein precipitation a material itself hemato-poietically active was released, rather than that there was just a separation of the intrinsic factor from the other constituents of the gastric juice. There was no reticulocytosis following this medication and no change in the clinical condition. After 2 other test periods this patient responded to Extralin, capsules 4 t. i. d., a. c. (reticulocytes 11% at a red blood cell level of 2.86 million) as is shown in Table 3.

Supernatant fluid from another casein precipitation of the gastric juice was then subjected to ultrafiltration. The ultrafiltrate (equivalent to 120 cc. of original juice) was incubated with 1 vial of liver extract and administered daily to Case 6. On the 7th day of this treatment the reticulocytes reached 14.1% (red blood cell count 2.03 million). There was a good rise in red blood cells, as is shown in Table 3, and definite clinical improvement. After 16 days the patient received for 3 days 3 cc. of concentrated liver extract intramuscularly. This was followed by a reticulocytosis up to 4.6% and a further rise in red blood cells.

The portion of this supernatant fluid that was held back by the ultrafilters was then diluted with water. In amounts equivalent to 120 cc. of the original gastric juice it was incubated with 1 vial of liver extract and administered daily for 10 days to Case 9. There was a rise in reticulocytes up to 6.6% by the 8th day (red blood cell count 2.58 million). There was definite clinical improvement and the red blood cell count made a very satisfactory increase (see Table 3). There was no subsequent rise in reticulocytes following the administration of Extralin.

In the studies in Section II it was shown that practically all the intrinsic factor in normal gastric juice had been held back by the ultrafilters. However, the experiments in Section IV demonstrate that after the precipitation of the pepsin and rennin and mucus by casein, a goodly portion of the intrinsic factor passes through the filters. This indicates that by the casein precipitation the intrinsic

TABLE 3.—THE RESPONSES OF THE BLOOD OF PATIENTS HAVING PERNICIOUS ANEMIA TO THE DAILY ADMINISTRATION OF ONE VIAL OF LIVER EXTRACT No. 343 INCUBATED WITH NORMAL HUMAN GASTRIC JUICE AFTER CASEIN PRECIPITATION OF THE GASTRIC JUICE.

Case number	7	8†	9
Age	63	56	45
Enzymes in original G. J. (aver. mg. per cc.)	Pepsin 5.2 Rennin 54.0	Pepsin 2.9 Rennin 32	Pepsin 4.9 Rennin 62
Enzymes in precipitate (aver. mg. per cc.)	Pepsin 3.7 Rennin 33.0	Pepsin 0 Rennin 0.1	Pepsin 0 Rennin 0.14
Enzymes in supernatant fluid (aver. mg. per cc.)	Pepsin 0 Rennin 0.05	Pepsin 0 Rennin 0.1	Pepsin 0 Rennin 0.14
Fraction of G. J. used	Precipitate	Supernatant fluid	Concentrate of supernatant fluid
Material derived from No. cc. G. J. incubated with 1 vial of L. E. No. 343	125	150 (no L. E.)	120
Days.	R. B. C. per cmm. Hgb. % *	R. B. C. per cmm. Hgb. % *	R. B. C. per cmm. Hgb. % *
0	2.01 2.05 2.13	2.19 2.28 2.20	2.24 2.37
1	0.5 44 40	3.7 49 46	3.5 45
2	1.2 51 44	4.0 43 44	3.4 45
3	1.2 44	5.3 44	2.4 47
4	1.5 44	5.3 44	2.8 47
5	1.8 47	10.2 50	6.5 43
6	3.6 47	9.5 46	7.4 49
7	3.4 47	22.0 46	10.4 53
8	3.4 49	29.8 43	14.1 57
9	3.7 40	38.3 46	10.8 53
10	3.5 40	37.4 46	7.9 55
11	3.5 40	1.65 41	10.0 55
12	3.5 40	20.0 41	7.1 55
13	3.5 40	20.0 41	6.1 55
14	3.5 40	20.0 41	3.6 55
15	3.5 40	20.0 41	3.6 55
16	3.5 40	20.0 41	3.6 55
17	3.5 40	20.0 41	3.6 55
Subsequent treatment	Conc. L. E., 3 cc. (3 daily doses)	Conc. L. E., 3 cc. (3 daily doses)	Conc. L. E., 3 cc. (3 daily doses)
0	2.25 41	2.19 49	2.24 44
1	2.25 41	2.19 49	2.24 44
2	2.25 41	2.19 49	2.24 44
3	2.25 41	2.19 49	2.24 44
4	2.25 41	2.19 49	2.24 44
5	2.25 41	2.19 49	2.24 44
6	2.25 41	2.19 49	2.24 44
7	2.25 41	2.19 49	2.24 44
8	2.25 41	2.19 49	2.24 44
9	2.25 41	2.19 49	2.24 44
10	2.25 41	2.19 49	2.24 44
11	2.25 41	2.19 49	2.24 44
12	2.25 41	2.19 49	2.24 44
Extralin, caps. 4 t. i. d.	3.11 59	3.11 59	3.11 59
Extralin, caps. 4 t. i. d.	3.11 59	3.11 59	3.11 59

* Newcomer method.

† This patient received 2 other test materials before responding to extralin.

factor was released or separated from some larger molecular material in the gastric juice, thus allowing it to pass through the filters.

Following these studies 400 cc. of normal gastric juice was precipitated at pH 4.7 with casein. The supernatant fluid, containing 0.08 mg. rennin per cc., was made up to pH 2 with HCl and passed through the ultrafilters and washed 3 times. This ultrafiltrate was then concentrated to 15 cc. by vacuum distillation. It was neutralized with NaOH and sterilized with tricresol and injected into Case 10 on June 22, 1933. At the beginning of the test the red blood cell count was 1.88 million, hemoglobin 35%, and reticulocytes 0.6%. There was a severe chill followed by a rise in temperature up to 104° F. The temperature remained elevated for 2 days. The reticulocytes reached 4.2% by June 26 and remained slightly above normal limits until July 2. By July 8 the red blood cell count was 1.71 million, hemoglobin 45.8%, and reticulocytes 0.9%. The patient then received 20 cc. of liver extract intravenously. This was followed by a reticulocytosis up to 20.6% by July 14. There was marked clinical improvement and by July 22, 1933, the red blood cell count was 3.15 million and the hemoglobin 51%.

The material concentrated by vacuum distillation in this test had been shown to contain a goodly amount of intrinsic factor (Case 6), and the process of concentration by vacuum distillation had previously always produced a hematopoietically active material when the intrinsic factor was present. It would therefore seem that by the casein precipitation and the ultrafiltration most of the material with which the intrinsic factor can react had been eliminated from the gastric juice.

Summary and Conclusions. From these studies it is quite evident that there must be some quantitative relationship between the amounts of intrinsic and extrinsic factors present to produce maximal reticulocyte responses when liver extract-gastric juice digests are fed to patients having pernicious anemia. The amount of intrinsic factor in from 50 to 75 cc. of normal gastric juice seems to be the minimal amount necessary to produce a maximal response when incubated with 1 vial of liver extract. The fact that as little as 10 cc. of normal gastric juice will increase the potency of 1 vial of liver extract enough to produce a slight reticulocytosis must, however, be considered when a quantitative estimation of the amount of intrinsic factor in an abnormal gastric juice is attempted, as by Hartfall, and Witts,⁶ Spies and Payne,⁷ and Beebe and Wintrobe.⁸ The use of liver extract as the source of the extrinsic factor in such tests now seems more advisable than the use of beef muscle, because if sufficient intrinsic factor is present in the gastric juice maximal reticulocytoses can be expected when 1 vial of liver extract is used, while this is not always the case when beef muscle is used.

The intrinsic factor in normal human gastric juice does not pass through the ultrafilters used in these experiments. The material in normal human gastric juice which can be made hematopoietically

active by concentration by vacuum distillation is likewise held back. It has therefore been shown that the intrinsic factor has been present at the onset of the concentration by vacuum distillation in all the gastric juice preparations that we have made active. The material in gastric juice concentrated by vacuum distillation which is active when injected, however, is not identical with the intrinsic factor, because the intrinsic factor is destroyed or used up by the process of concentration by vacuum distillation during which the active material in concentrated gastric juice is formed. However, the ultrafiltrate of gastric juice freed from pepsin, rennin, and mucus by casein precipitation but containing the intrinsic factor, was not hematopoietically active after concentration by vacuum distillation. This would tend to support the hypothesis that the hematopoietically stimulating material in concentrated normal human gastric juice is not formed unless both an intrinsic and an extrinsic factor are present in the gastric juice during the process of concentration by vacuum distillation.

These experiments confirm the work of Castle and his associates in that the intrinsic factor can be separated from the enzymes pepsin and rennin by casein precipitation. They also tend to show that the intrinsic factor is of relatively small molecular structure after it is freed from the pepsin, rennin, and mucus by the casein precipitation.

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THE RÔLE OF THE LIVER IN HEMATOPOIESIS.

By S. MILTON GOLDHAMER, M.D.,

INSTRUCTOR,

RAPHAEL ISAACS, M.D.,

ASSOCIATE PROFESSOR,

AND

CYRUS C. STURGIS, M.D.,

PROFESSOR OF INTERNAL MEDICINE, UNIVERSITY OF MICHIGAN,

ANN ARBOR, MICH.

(From the Thomas Henry Simpson Memorial Institute for Medical Research,
University of Michigan.)

DURING recent years a series of observations on the treatment of pernicious anemia has helped to clarify many points concerning the normal physiology of the liver and its relation to blood forma-

tion. Beginning with the work of Minot and Murphy,¹ in 1926, on the beneficial effect of liver substance in the treatment of pernicious anemia, subsequent workers² have demonstrated that a similar response could be obtained by the feeding of desiccated defatted hog stomach. The hypothesis was that after eating ground, dried stomach, a material was produced which was converted into a material similar to that derived from liver, and the excess was stored in the hepatic tissues. Richter, Ivy and Kim³ concluded that the "active substance" was not an integral part of liver tissue, but a storage product which could be released when needed, to govern hematopoiesis. Confirmatory evidence of the function of the liver as a storehouse rather than as a source of a specific protein or some other substance contained in its own cellular makeup was obtained by the finding of livers which did not contain the "active material." The clue to this was given by the fact that some patients with cirrhosis of the liver had an anemia with red blood cells larger than normal. Others, with evident hemorrhage, simulated the "secondary" types of anemia.

The following experiments were developed to (1) explain why some patients with disease of the liver developed an anemia with large red blood cells, and (2) to note the curative effect of adequate therapy with liver extract on this type of anemia.

Materials and Methods. The patients studied in these experiments were classical cases of pernicious anemia, as evidenced by finding in all of an achylia gastrica, characteristic blood pictures, and definite clinical features as glossitis and neurologic changes. The blood counts were made with pipettes certified by the U. S. Bureau of Standards. Hemoglobin estimations were made with Leitz hemoglobin standard, calculated so that 14 gm. = 100%. This was checked in accordance with van Slyke's gas method. The immature red cells (reticulocytes) were studied from films stained with the vital dye, brilliant cresyl blue. All the extracts were prepared from human livers, according to the chemical method previously described.⁴ Control periods of at least 2 days were obtained in each instance to rule out the possibility of spontaneous remissions.

The Active Principle Present in Liver Tissue at the Time of Birth or Shortly Before. Experiment I. A chemically refined extract was prepared from a 7-month human fetal liver. The final dosage of 20 cc., representing 65 gm. of fresh liver, was administered to a patient with typical pernicious anemia, whose blood picture on admission was as follows: Red blood cell count, 950,000 per cmm.; white blood cell count, 3600 per cmm.; hemoglobin, 25% (Sahli). On the 7th day following treatment a reticulocyte peak of 17.6% was noted. Although the maximum calculated reticulocyte response⁵ was not obtained, the results are certainly indicative that at 7 months a human fetal liver contains the active principle necessary for red cell development. (Chart 1.)

The Active Principle Absent From the Liver of an Inadequately Treated Case of Pernicious Anemia. Experiment II. A parenteral extract was prepared, similar to the above described, from the human liver of a patient with pernicious anemia, who had shown only slight improvement with antianemic therapy, and died subsequently with severe complications. On admission his red cell count was 2,100,000 per cmm.; hemoglobin, 58% (Sahli, 14 gm. = 100%); the film showed marked poikilocytosis and anisocytosis with 58.5% of the red cells larger than 7.5 microns.

This intravenous product was given to a patient with pernicious anemia, whose red cell count was 1,560,000 per cmm.; white blood cell count, 6900 per cmm.; hemoglobin, 29% (Sahli). No response was noted after an interval of 12 days. When a known potent parenteral extract was administered later to this same patient, a maximum reticulocyte response of 52.8% was obtained. The absence of any response following the initial treatment was probably the result of the failure of the body of the patient from whom the liver was taken to produce or store the necessary hematopoietic factor. A similar experiment was performed by Richter *et al.*,³ who also demonstrated that a liver from an inadequately treated case of pernicious anemia did not contain the active principle. (Chart 2.)

The Active Principle Present in the Liver of an Adequately Treated Case of Pernicious Anemia. Experiment III. A third extract was prepared from the liver of a patient with pernicious anemia who received a maximum amount of treatment for a period of 18 days, but died following an operation. At the time of admission the red cell count was 2,900,000 per cmm.; hemoglobin, 53% (Sahli). Five days after therapy was started the reticulocytes reached a maximum response of 12.5%. When this preparation was administered intravenously to a patient having pernicious anemia (red blood cell count, 1,630,000 per cmm.; white blood cell count, 4500 per cmm.; hemoglobin, 41%), a prompt subjective improvement resulted as well as a maximum reticulocyte response of 21.9%. This experiment, demonstrating the presence of the active principle in the liver of a patient with pernicious anemia, who had adequate therapy, fully substantiates the work of Richter, Ivy and Kim. (Chart 3.)

A Cirrhotic Liver May Not Contain the Active Principle. Experiment IV. A human liver was obtained from a patient dying of atrophic cirrhosis of the liver. His blood on preliminary examination showed a red count of 1,050,000 cells per cmm.; white blood cells, 3500 per cmm.; hemoglobin, 28% (Sahli). Red cell measurements revealed a Price-Jones curve simulating that seen in pernicious anemia. A chemically purified extract was prepared in the usual manner, and given to a pernicious anemia patient with no subsequent clinical improvement or blood changes. At the time of admission her blood picture was as follows: Red blood cell count, 2,400,000 per cmm.; white blood cell count, 9200 per cmm.; hemoglobin, 62% (Sahli). After a lapse of 7 days, the same individual was treated with a known potent intravenous liver extract. Ninety-six hours after therapy was instituted, the reticulocytes reached a maximum peak of 10.8% and was accompanied by the usual symptomatic improvement. (Chart 4.)

The absence of the hematopoietic substance necessary for the maturation of the red cells is certainly suggestive that a cirrhotic liver is unable to store this material since the patient with cirrhosis also showed evidence of a lack of "active material." As will be shown later, a damaged liver may have the normal function for storage of the active principle, but for some unknown reason is unable to present it to the tissues for utilization.

Patients With Cirrhosis of the Liver and Macrocytic Anemia Respond to Parenteral Liver Extract Therapy. Experiment V. Two patients with cirrhosis of the liver (diagnosed at operation), having blood pictures simulating pernicious anemia—Case 1: red blood cell count, 1,740,000 per cmm.; white blood cell count, 3800 per cmm.; hemoglobin, 44% (Sahli); and Case 2: red blood cell count, 2,220,000 per cmm.; white blood cell count, 11,100 per cmm.; hemoglobin, 41% (Sahli)—were treated post-operatively with known potent parenteral liver extracts.⁵⁻⁹ In each instance, a maximum reticulocyte response was obtained, being 36.4% and 11% respectively. One of these patients has received parenteral therapy for a period of 2 years with no recurrence of the anemia or any of

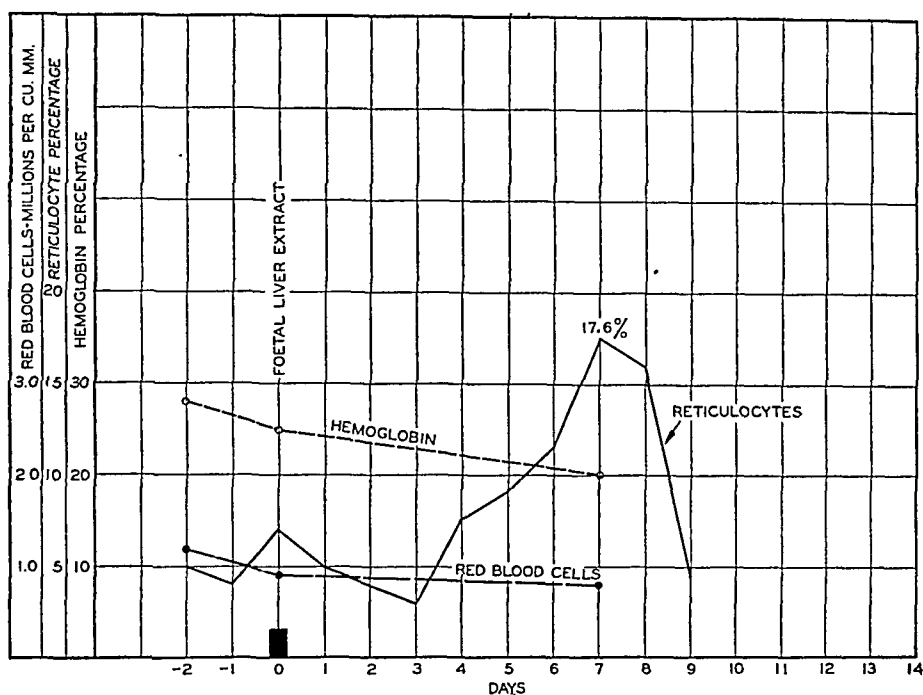


CHART 1.—Reticulocyte response with human fetal liver extract (65.0 grams.)

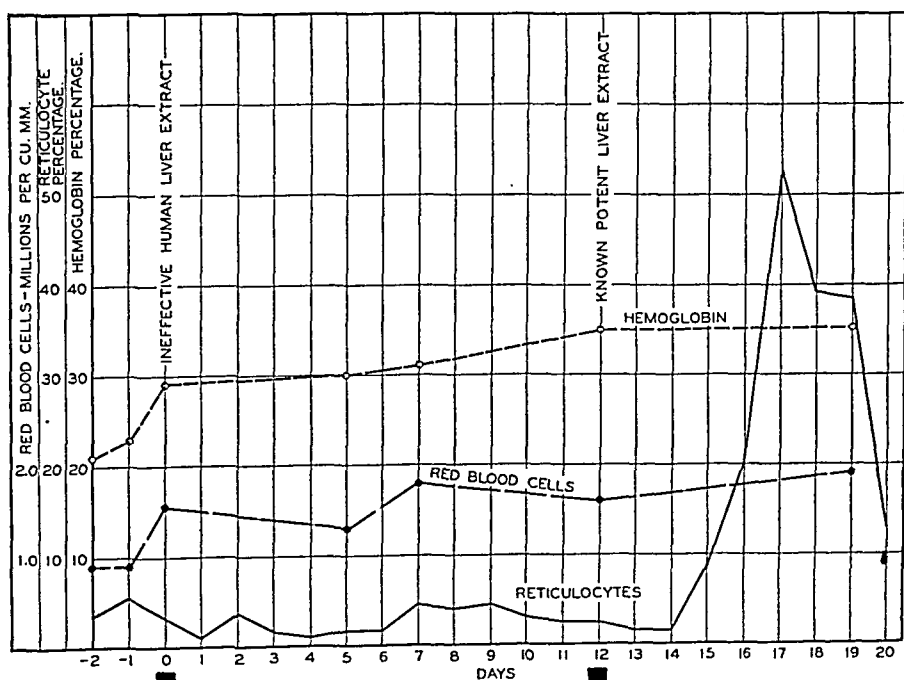


CHART 2.—Liver from inadequately treated case of pernicious anemia—not effective.

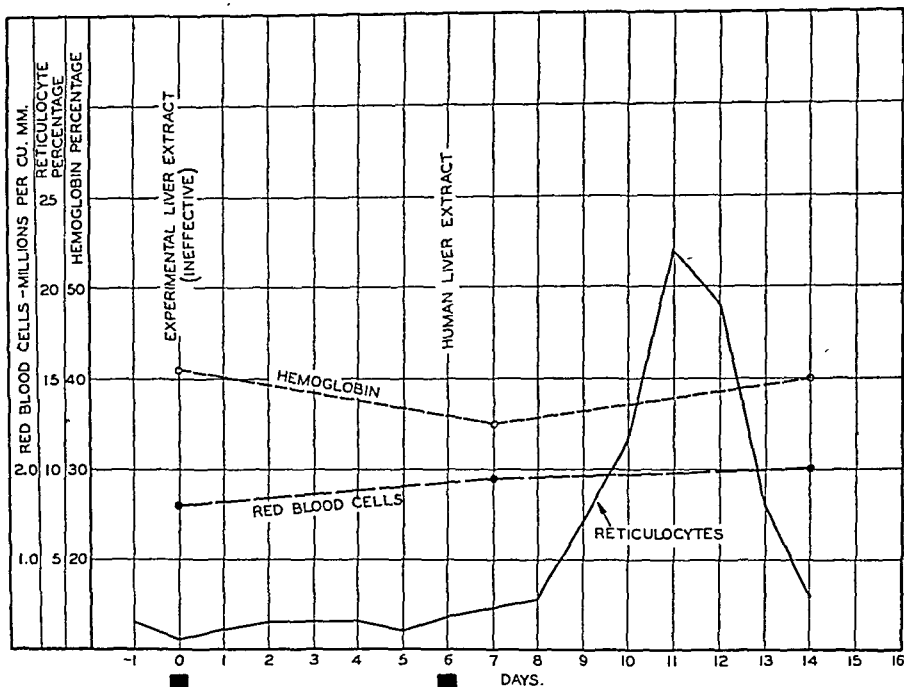


CHART 3.—Liver from adequately treated case of pernicious anemia—effective.

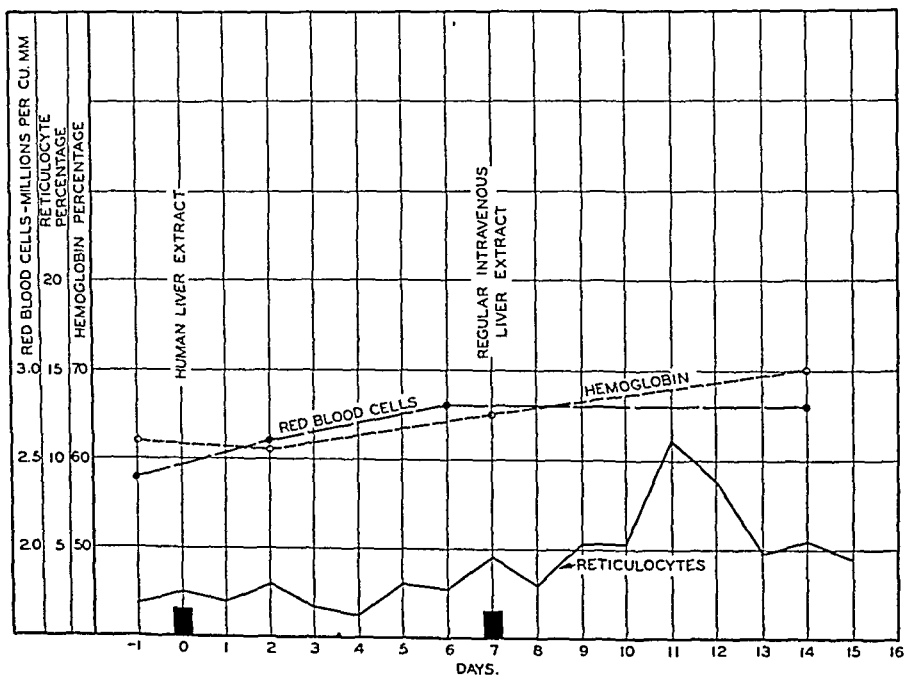


CHART 4.—Failure of response from cirrhotic liver.

its symptoms. It has not been possible to follow the second patient as he has not returned.

The Inability to Utilize the Active Principle, Even Though It is Stored, Suggesting a Fifth Factor in the Production of a Macrocytic Anemia. Experiment VI. An intravenous extract was made from the liver of a patient who had had acute yellow atrophy. On admission his red cell count was 2,450,000 per cmm.; hemoglobin, 54% (Sahli); 51% of the red cells were larger than 7.5 microns. When the parenteral extract prepared from this liver was given to a patient with pernicious anemia (red blood cell count, 1,530,000 per cmm.; hemoglobin, 41% (Sahli)), a maximum reticulocyte response of 34.6% was produced.

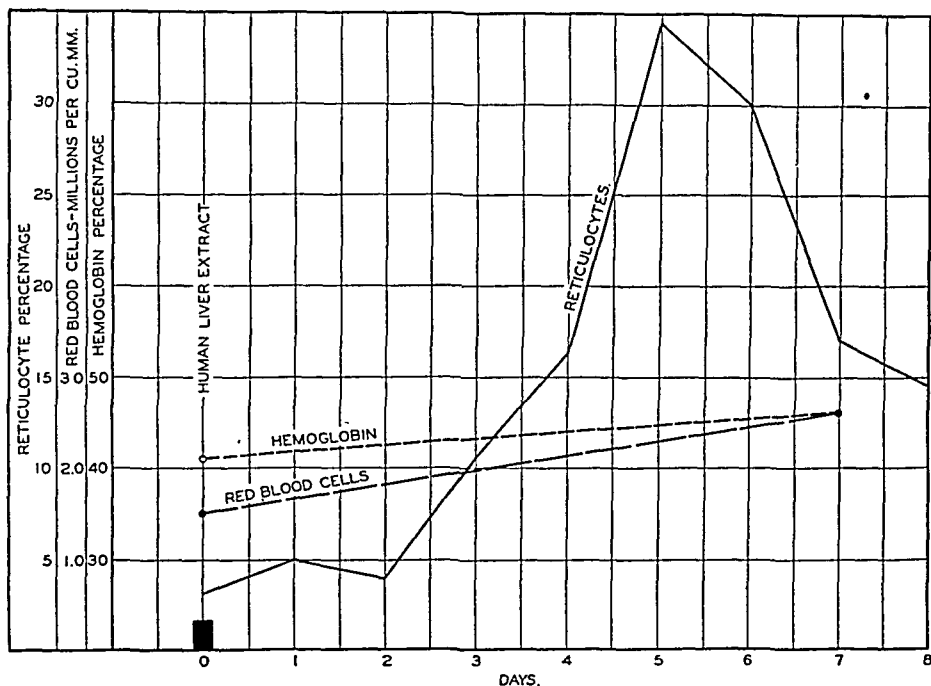


CHART 5.—Liver damaged from acute yellow atrophy—effective.

Although the unknown substance was present in the acutely damaged liver, for some unknown reason the patient with the acute yellow atrophy probably was unable to utilize it, as was evidenced by the severe macrocytic anemia which was present. This disturbance of metabolism by the liver is to be differentiated from the inability of storage as suggested in Experiment IV. (Chart 5.)

Discussion. From the above experiments, as well as those previously described by other authors,^{3, 10} it can be concluded that liver tissue is primarily a storehouse for the hematopoietic substance necessary for the maturation of red cells. It is also highly suggestive that, although the active principle may be present in the liver, if sufficient hepatic damage is present, this organ is unable to release the necessary substance for red cell development in a suit-

able form for utilization by the body tissues. Thus, if for any reason, there is marked injury to the liver (cirrhosis, acute yellow atrophy), the normal hematopoietic rôle of the liver is disturbed and a macrocytic anemia may develop, though the stomach may make the necessary material.¹⁰ This resulting blood picture may be clouded by a so-called "secondary anemia" with a low color index, due to gastro-intestinal bleeding. As previously mentioned, the macrocytic anemias, associated with cirrhosis of the liver, have been controlled by parenteral liver extract.^{9, 10} Recently, Cheney⁸ has suggested the use of "secondary anemia" liver extract and iron in the treatment of similar cases.

Conclusions. 1. The active principle necessary for the maturation of red cells is present in the liver at least 2 months before birth.

2. The active principle may be absent from the liver of an inadequately treated case of pernicious anemia.

3. The active principle is present in the liver of an adequately treated case of pernicious anemia.

4. A cirrhotic liver may not contain the active principle.

5. It is highly suggestive that a liver may be sufficiently damaged so that the active principle, though present, cannot be presented to the tissues for utilization.

6. A pernicious anemia-like blood picture may be present in a patient, if the liver is so damaged that it cannot store the active principle, or cannot present it to the body tissues in the proper form for utilization.

7. The demonstration that all livers do not contain the "active principle" indicates that it is a storage product rather than an intrinsic part of the liver substance.

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THE RELATION BETWEEN DEFICIENCY OF SOLAR RADIATION AND MORTALITY DUE TO PERNICIOUS ANEMIA IN THE UNITED STATES.

BY JAMES H. SMITH, M.D.,
RICHMOND, VA.

(From the Medical Department, McGuire Clinic, St. Luke's Hospital.)

THE purpose of this article is to compare the amount of solar radiation with the mortality due to pernicious anemia in the states of the United States.

I. The total radiation received on a unit of horizontal surface from the sun and sky has been measured for 17 stations.¹ Kimball's report shows: (a) The annual march of daily totals of radiation, and (b) the average annual amounts of solar thermal energy received at these stations. The values are expressed as kilowatt-hours per square dekameter of horizontal surface. The stations for which climatic data are available for comparison with the measurements referred to, with a view to arriving at an index applicable to all weather bureau stations in the United States, are Madison, Wis., Lincoln, Neb., Washington, D. C., and Havana, Cuba. From Kimball's tables and reading from his charts, the measured data are shown in Table 1 (a). The data selected for comparison are shown in Table 1 (b). In this table a radiation index is calculated by dividing by 3 the sum of the angle of incidence of the sun's rays, the percentage of possible sunshine² and 100 minus the P.M. mean relative humidity.² One unit of this index is roughly equivalent to 3150 kw.-hr. per sq. dkm. *per annum* for the 3 United States stations.*

Chart I shows the correlation between the measured amounts of solar energy and the radiation index. The comparison appears to show a fairly close approximation and to warrant the use of the radiation index, so calculated, for the purpose at hand.

II. The average annual death rate from pernicious anemia per 100,000 estimated population in the registration area of the United States for the years 1921 to 1926 inclusive (prior to the therapeutic use of liver) is shown by states in Table 2³ and is traced in Chart II. In comparison, Chart II shows also the radiation index for the corresponding states calculated as described above. The average of all stations reporting is used to compute the percentage of possible sunshine and the relative humidity for each state. From this comparison the following general statements may be made: The death rate from pernicious anemia is high in proportion to the radiation index in the western states with high altitude, high radiation index and relatively low latitude; the death rate is low in proportion to

* Madison 3171, Lincoln 3197, Washington 3117, Havana 3500. Figures for sunshine at Havana were not available and those for Key West, Florida, were used instead.

TABLE 1.—SOLAR ENERGY PER UNIT OF HORIZONTAL SURFACE.

(a) Measured Values (After Kimball).

	Latitude.		Longi- tude.		Altitude. Meters	Kilowatt-hours per square dekameter. Daily mean.												Annual.
	N °	'	W °	'		J	F	M	A	M	J	J	A	S	O	N	D	
Madison	43	05	89	23	308	192	277	362	451	541	603	588	500	389	268	173	146	139,523
Lincoln	40	50	96	41	381	243	340	435	507	577	654	653	569	462	343	247	203	160,906
Washington	38	56	77	05	137	194	276	376	467	544	572	548	498	424	332	225	169	145,493
Havana	23	09	82	21	40	374	457	569	613	587	618	637	565	507	425	341	333	184,488

(b) Index for Comparison with Measured Values.

Madison:																			
A—Angle of incidence of sun's rays	30	38	46	54	62	70	62	54	46	38	30	23*	46†						
S—Percentage of possible sunshine	43	52	55	53	57	64	69	64	58	50	42	38	54						
H—100 minus S p.m. mean relative humidity	21	25	31	39	40	35	40	37	32	33	28	21	32						
R—Radiation index $\frac{(A+S+H)}{3}$	31.3	38.3	44.0	48.7	53.0	56.3	57.0	51.7	45.3	40.3	33.3	27.3	44.0						
Lincoln:																			
A—	32	40	48	56	64	72	64	56	48	40	32	25	48						
S—	57	59	62	59	62	72	76	72	63	61	58	54	63						
H—	29	32	42	48	45	45	48	44	42	43	37	29	40						
R—	39.3	43.7	50.7	54.3	57.0	63.0	62.7	57.3	51.0	48.0	42.3	36.0	50.33						
Washington:																			
A—	34	42	50	58	66	74	66	58	50	42	34	27	50						
S—	47	54	55	58	61	62	64	61	64	61	55	49	58						
H—	33	37	39	42	42	30	29	26	24	28	34	34	32						
R—	38	44.3	48.0	52.7	56.3	55.3	53.0	48.3	46.0	43.7	41.0	36.7	46.67						
Havana:																			
A—	50	58	66	74	82	90	82	74	66	58	50	43	66						
S—	68	74	77	79	74	67	68	70	62	60	66	66	69						
H—	23	24	27	27	24	20	22	21	19	21	21	23	23						
R—	47.0	52.0	56.7	60.0	60.0	59.0	57.3	55.0	49.0	46.3	46.0	44.0	52.67						

* Approximate.

† At equinox.

‡ Figures from Havana not available.

TABLE 2.—RADIATION INDEX AND MORTALITY DUE TO PERNICIOUS ANEMIA, BY STATES.
Radiation Index Above 51.

States.	Lat.	Alt.	Rad. Ind.	Minus Lat. subtracted from 49.	Corrected Rad. index.	P. A. mortality.	Comments.	
Group A.								
(States in order of ascending latitude)								
Arizona	34	2700	68.0	15.0	53.0	2.7	Altitude: Mean of stations reporting. Mortality from pernicious anemia per 100,000 estimated population 1921-1926 inclusive.	
California	37 30	520	54.2	11.5	42.7	7.5		
Kansas	38 30	1700	53.8	10.5	43.3	6.9		
Colorado	39	4800	59.3	10.0	49.3	6.0		
Utah	39 30	4850	58.8	9.5	49.3	5.0		
Nebraska	41 30	1870	51.2	7.5	43.7	6.9		
Group B.								
(States in order of descending altitude)								
Wyoming	43	5350	52.6	2.8	Iowa: The instance of greatest discrepancy between radiation index and mortality from pernicious anemia. New Hampshire: Climatic data estimated. See Vermont.	
Idaho	44	3550.	55.3	3.0		
Radiation Index Below 51.								
Altitude 3000 to 520 feet. (Group B, no correction.)								
Montana	47	2950	46.6	4.3		
North Dakota	47 30	1600	45.5	5.6		
Oregon	44	1330	46.6	6.6		
Minnesota	46	970	43.0	9.7		
Missouri	38 30	860	49.5	4.7		
Iowa	42	800	46.6	10.4		
Vermont	44	800	37.7	9.2		
New Hampshire	44	800	37.7	9.4		
Wisconsin	45	700	44.3	9.0		
Kentucky	37 30	700	48.8	2.8		
Ohio	40 30	680	45.5	6.0		
Michigan	44 30	640	40.2	9.7		
Indiana	40	640	47.3	6.4		
Tennessee	36	600	49.3	2.8		
Illinois	40	520	47.3	6.2		

	Lat.	Alt.	Rad. Ind.	Plus Lat. subtracted from 49.	Corrected Rad. index.	P. A. mortality.	
GROUP A REVERSED.							
West Virginia	38 30	1250	41.5	10.5	52.0	3.5	Unique in low percentage of sunshine and high humidity for altitude (1250 feet) of reporting stations. It is treated like Group A except that the correction is an addition rather than a subtraction.
GROUP C.							
(States in order of descending altitude)	Lat.	Alt.	Rad. Ind.	Plus 2 + Alt. in terms of 100 ft.	Corrected Rad. index.	P. A. mortality.	
Altitude below 520 feet. (Group C, addition for altitude.)							
Virginia	37 30	516	45.5	7.0	52.5	2.5	Virginia: Altitude includes Washington, D. C.
Pennsylvania	41	500	44.0	7.0	51.0	4.7	
Washington	47 30	450	39.8	6.5	46.3	6.3	
New York	43	380	41.3	5.8	47.1	5.5	
Georgia	33	340	50.3	5.4	55.7	1.4	Delaware: Climatic data estimated; see Maryland.
Alabama	33	300	49.7	5.0	54.7	1.2	
Mississippi	33	250	50.7	4.5	55.2	1.0	
North Carolina	35 30	250	48.5	4.5	53.0	1.6	
South Carolina	34	150	49.7	3.5	53.2	1.2	D. C. urban area.
Louisiana	31	100	49.6	3.0	52.6	1.7	
Maryland	39	100	47.7	3.0	50.7	3.7	
Delaware	39	100	47.0	3.0	50.0	3.8	
Connecticut	41 30	100	44.5	3.0	47.5	5.3	D. C. urban area.
Maine	45	50	40.7	2.5	43.2	7.7	
Massachusetts	42 30	50	42.5	2.5	45.0	7.3	
Rhode Island	41 30	50	42.2	2.5	44.7	5.9	
New Jersey	40	50	45.3	2.5	47.8	4.3	D. C. urban area.
Florida	29	0	49.7	2.0	51.7	3.8	
District Columbia	39	100	47.0	3.0	50.0	5.6	

the radiation index in the eastern and southern states with relatively low radiation index and low altitude; and the death rate is neither high nor low in proportion to the radiation index in the central states with altitude neither high nor low. These variations may represent either the inaccuracy of the index or an effect of altitude in increasing the death rate from pernicious anemia. There are recognized physiologic responses of the blood to increased altitudes, including increased number of red blood cells.

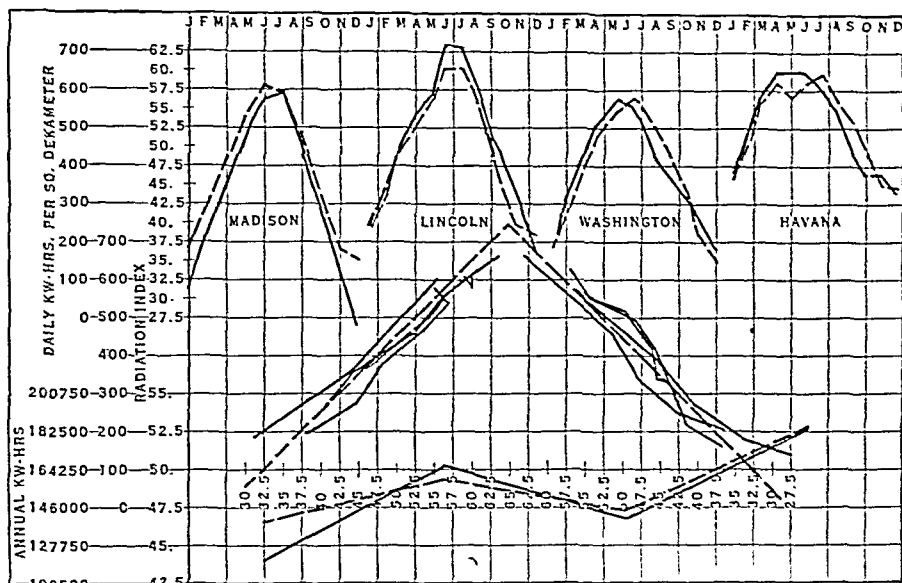


CHART I.—The upper series of 4 pairs of curves shows approximately the monthly march of mean daily totals of radiation received on a horizontal surface directly from the sun and diffusely from the sky, broken line (after Kimball) and the radiation index, continuous line, calculated for each month as described in the text. The central group of curves shows the same data plotted as a scatter diagram with the monthly points for each station connected by a solid line. The mean standard is represented by a broken line. The lower pair of curves represents the comparison between annual measurements (broken line) and the radiation index (continuous line) for each of the 4 stations.

The curve of corrected radiation index shown in Chart II is according to the principles embodied in Table 2. Since the corrections are on the basis of latitude and altitude, it would seem that they can be made in conformity with the concept of the index. However, with reference to either the uncorrected or the corrected index, comparison of states with each other within the 3 chief groups would seem to show a significant correlation between deficiency of solar radiation and mortality due to pernicious anemia.

Conclusions. 1. For the geographic and climatic conditions represented by Madison, Wis., Lincoln, Neb., and Washington, D. C., in the United States, and Havana, Cuba, the solar energy received per month and *per annum* is represented with fair accuracy by the

result of dividing by 3 the sum of the angle of incidence of the sun's rays at the equinox, the percentage of possible sunshine and 100 minus the mean relative humidity at about 8 P.M.

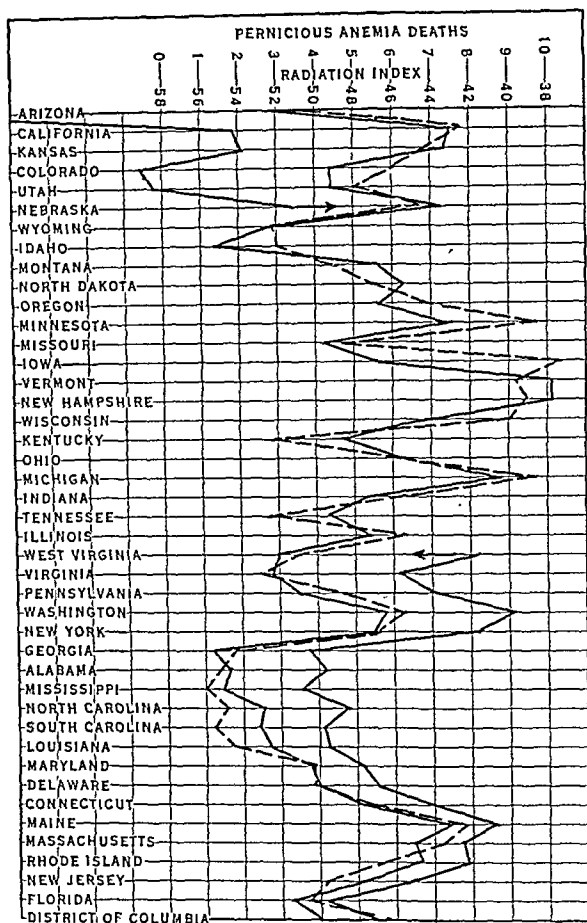


CHART II.—The scale for radiation index is reversed to make a low index comparable with height on the scale of mortality from pernicious anemia. The broken line indicates mortality from pernicious anemia, the continuous lines indicate radiation index. The curve of radiation index is uncorrected between the two arrows and on the left below and on the right above. Where it is continuous with the central portion it is corrected in its range to left and right of arrows as shown in Table 2.

2. The data presented are considered to show a significant relationship between relative lack of solar radiation and mortality from pernicious anemia in the United States prior to the introduction of the therapeutic use of liver.

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BILE PIGMENT AND HEMOGLOBIN REGENERATION.

THE EFFECT OF BILE PIGMENT IN CASES OF CHRONIC
HYPOCHROMIC ANEMIA.*

BY ARTHUR J. PATEK, JR., M.D.,

RESEARCH FELLOW IN MEDICINE, HARVARD UNIVERSITY; ASSISTANT RESIDENT
PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL,

AND

GEORGE R. MINOT, M.D.,

PROFESSOR OF MEDICINE, HARVARD UNIVERSITY; DIRECTOR, THORNDIKE MEMORIAL
LABORATORY; VISITING PHYSICIAN, BOSTON CITY HOSPITAL,
BOSTON, MASS.(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services
(Harvard) of the Boston City Hospital, and the Department of Medicine,
Harvard Medical School.)

NUMEROUS investigators have studied the problem of pigment metabolism and debated whether any of the bile pigment that flows into the intestine is conserved by absorption for some purpose associated with hemoglobin regeneration. There is no definite agreement as to whether or not bile pigment can be absorbed and utilized by the body for this purpose. The studies have been made largely on animals and not on patients with anemia. From experimental work with bile-fistula dogs, Whipple¹ and his coworkers conclude that bile pigment is a waste product. By injecting hemoglobin or by feeding bile^{3,4} to dogs in good nutritional condition but rendered anemic by chronic blood loss, a failure to gain in hemoglobin and a recovery of the bile pigment indicated that pigment was not conserved. Although Blankenhorn⁵ and other investigators⁷ found that, in dogs, bilirubin as such is not absorbed from the intestine, they have indicated that other bile pigments may be taken into the body from the intestinal tract. The studies of Broun, McMaster and Rous⁸ and other observers^{9,10} support the contention that bile pigment can be absorbed from the intestine for building hemoglobin. The former authors showed that after feeding sheep bile to dogs it could be recovered in the dogs' bile. Furthermore, it has been demonstrated in animals that chlorophyll^{11,12} and related pyrrol substances¹³ can be absorbed so as to influence favorably the regeneration of hemoglobin.

Ever since Virchow¹⁴ identified the chemical similarity between hematoidin and bilirubin in blood extravasations, there has been an implied interrelationship between hemoglobin and bile pigment metabolism. Where blood destruction is prominent as in hemolytic jaundice, it is well recognized that the increased excretion of bile

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pigment is due largely to the rapid liberation of hemoglobin from the red cells. An increased excretion of bile pigment, as in pernicious anemia, may depend in part upon an inability of the body to utilize pigment-forming substances, not necessarily derived from excessive red blood cell breakdown. Studies, which are less widely appreciated, indicate that the amount of bile excretion is diminished by blood loss and conversely that loss of bile through fistula may result in anemia. For example, Whipple² has shown that dogs rendered anemic by repeated hemorrhage excreted less bile than normal dogs. McMaster, Broun and Rous¹⁶ and Seyderhelm¹⁶ note that dogs with biliary fistulae, and presumably without bartonella infection, develop anemia, although Whipple does not concur in these findings. There has been disagreement as to the technique, results, and interpretation, but in the final analysis it seems likely that an interplay of some sort occurs between the factors for hemoglobin formation and bile pigments. It is not implied that because hemoglobin is a precursor of bile pigment, the reverse must take place, but it is felt, in view of studies to be described, that bile pigment probably plays a rôle in hemoglobin formation.

It would be hazardous to make literal translation to human disease of evidence coming solely from the unnatural conditions imposed by animal studies. In addition to the experimental data, however, there is clinical evidence supporting the hypothesis that bile pigment may be concerned in hemoglobin formation. Decreased pigment content of the plasma in "secondary anemia" has been known for a long time. As Whipple¹⁷ says: "Secondary anemia in direct contrast to pernicious anemia is a disease in which there is a deficit of hemoglobin pigment and related pigments." The low icteric index of uncomplicated cases of hypochromic anemia stressed by Meulengracht,¹⁸ and the decreased bile pigment excretion in the stools as noted, for example, by Addis¹⁹ imply a pigment want in these patients.

The oral administration of adequate amounts of inorganic iron can cause rapid hemoglobin regeneration in many patients with hypochromic anemia. Iron given parenterally²⁰ may be recovered in the blood almost quantitatively in an organized form—hemoglobin; but as the hemoglobin rises, there tends to be a greater discrepancy between the amount of iron injected and the amount of hemoglobin formed. Iron cannot, of course, by itself make hemoglobin. Copper, and apparently other mineral elements,^{21,22,23} may supplement the effectiveness of iron in rats rendered anemic by milk diet; but something more than minerals is required to form the complex hemoglobin molecule. Certain amino acids may affect hemoglobin regeneration,²⁴ and a deficiency of these might play a rôle in disease, so that a proper supply might facilitate the building of a portion of the hemoglobin molecule. In hypochromic anemia where iron is so effective, the body may perhaps retain a sufficient

supply of factors other than iron from which to make hemoglobin. However, it is reasonable to suppose that in some cases these factors, too, are deficient; or if they are not actually deficient, perhaps an inability to utilize them may exist. Theoretically, also, some abnormality in the utilization of iron may occur which might be overcome when a suitable supply of other hemoglobin-building substances is made available.

In chronic hypochromic anemia there is often more than one etiologic factor; dietary deficiency, faulty gastro-intestinal function, including achlorhydria, blood loss and pregnancy—all may play a rôle in causation. Thus, there are numerous opportunities for deficiencies in the body of other material than iron necessary for the synthesis of hemoglobin.

With adequate iron therapy certain patients with hypochromic anemia are unable to reach or maintain a hemoglobin concentration of more than about 75% of normal, when evidence of inhibitory factors, such as infection, is lacking. Occasionally in such cases, the addition of liver, rich in pigment pyrrols, satisfies the gap.^{25,26} Whipple¹⁷ has shown clearly that liver harbors material which independently of iron, is potent for blood regeneration in hypochromic anemia due to hemorrhage. This substance is different from the substance in liver effective for pernicious anemia.

Presumably factors for the construction of the globin portion of hemoglobin are contained in any diet that is not lacking in suitable protein, and perhaps the same may be true for the hematin portion—a pigment pyrrol component. There is indirect evidence, however, that this portion is more necessary to the body economy. Since bile pigment is diminished in cases of hypochromic anemia and since it is rich in the hemopyrrol material found in hemoglobin, it was decided to determine what hemopoietic effect, if any, concentrated bile pigment might exert in human chronic hypochromic anemia. These cases are most satisfactory ones in which to estimate the value of material for hemoglobin regeneration. This is not only because of the relatively much greater reduction of hemoglobin than red blood cells, but also because such cases do not develop “spontaneous” improvement in their blood, except occasionally, and then only very slowly.

Methods. Reticulocyte counts were made daily on capillary blood. Hemoglobin and red blood cell counts were determined from venous blood every 2 or 3 days. The hemoglobin was estimated from an average of two readings with Sahli hemometers, standardized by van Slyke oxygen capacity determinations, so that 15.6 gm. of hemoglobin per 100 cc. corresponded to a capacity of 21 volumes of oxygen %.

Before the observations reported here on the effects of concentrated bile pigment were begun, the same sort of observations were made with ox bile (*fels bovis*, U.S.P.) on 6 cases of chronic hypochromic anemia. When about 2 gm. daily were given, responses of the same sort as reported below were obtained, but their magnitude was slight. This amount of

fels bovis often caused epigastric distress and diarrhea, presumably from the bile salts. Diarrhea, of course, could prevent absorption and lead to dehydration, thus confusing hemoglobin values. Therefore, a preparation relatively free from salts was sought after, for it was believed that the hemopoietic effect noted had been due to pigment rather than bile salts, as claimed by Seyderhelm.²⁷ Eli Lilly and Company kindly made the concentrated preparation of bile pigment used by a process briefly described as follows: Beef bile was made alkaline with ammonium hydroxide and a concentrated solution of calcium chloride added to the point of complete precipitation. The precipitate was centrifuged off and washed with water, 10% acetic acid, a mixture of acetone and ether, and ether. The residue was then dried quickly *in vacuo*. This provides a product essentially free of bile salts, inorganic salts, cholesterol, fats and mucin. On chemical analysis only traces of iron were present.

The pigment was administered in capsule form because of its bitterness. No toxic or undesirable effects took place.

Nine selected cases of chronic hypochromic anemia were fed the concentrate of bile pigment. The first 8 cases had not been treated. The patients were given the usual hospital fare, excepting meat and eggs. After about 5 days' observation, during which time the blood values were unaltered, each patient was given daily about 2 gm. of the bile pigment for an average of 6 days. No other medication was used until a 10-day period had been fulfilled.

A second period of 10 days followed directly, during which iron and ammonium citrate was given in daily doses, usually of 0.5 gm. In a third period the same daily dose of iron was continued, and in addition bile pigment in about the same amount as before. Thus, there were 3 sets of observations, namely, on the effects of bile pigment, on small doses of iron, and on iron with bile pigment. All medication was given by mouth and the same vehicle, either milk or orange juice, was used throughout the observations on the one case. Two sets of observations were also made on the effect of bile pigment in a patient (Case 9) with idiopathic hypochromic anemia, who had been unable to regain a normal hemoglobin level in spite of large doses of iron for many months.

Results. Table 1 records synoptically the observations on the effect of bile pigment, iron, and iron with bile pigment successively. It is emphasized that this tabulation begins after an observation period without therapy when the reticulocytes and hemoglobin remained remarkably constant. In the first period with bile pigment there occurred a rise of hemoglobin unaccompanied by a change in the reticulocytes. The hemoglobin rise in 10 days was usually about 6%, and in Case 4 was 15%.

The second period with a distinctly suboptimal daily dose of iron and ammonium citrate follows directly; that is to say, the second day of this period was 2 days after the last observation recorded in Period 1. The only notable effect here is that with considerable regularity, there occurred a small reticulocyte response, although in Case 2 a relatively rapid and large response took place. During this period the hemoglobin concentration in each case, except Case 2, remained practically constant for 10 days. In Case 2, with the unusually pronounced reticulocyte response to a small dose of iron, the hemoglobin rose 10% between the 10th and 20th days.

TABLE 1.—THE ORAL ADMINISTRATION TO 8 CASES OF HYPOCHROMIC ANEMIA OF FIRST, BILE PIGMENT; SECOND, IRON AND AMMONIUM CITRATE; AND THIRD, A COMBINATION OF THESE TWO.

Bile Pigment Alone.

Days of treatment.	Case 1.		Case 2.		Case 3.		Case 4.		Case 5.		Case 6.		Case 7.		Case 8.	
	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %
0	48	1.1	40	1.1	64	0.9	44	1.1	45	0.8	42	0.8	40	0.5
2	49	1.7	43	0.8	65	0.7	46	0.8	45	0.6	42	0.9	42	0.6
4	51	1.4	43	0.9	67	0.7	50	1.1	45	1.2	44	1.2	42	0.4
6	56	1.1	42	1.8	68	1.0	52	0.8	46	0.8	45	1.1	44	0.6
8	56	1.0	46	1.1	69	1.2	52	0.9	48	0.4	45	1.1	46	1.0
10	48	1.7	70	0.7	59	0.9	50	0.5	46	1.2	46	1.1

Iron and Ammonium Citrate Alone.

	0.4 gm. daily.		0.5 gm. daily.		0.4 gm. daily.		0.4 gm. daily.		0.4 gm. daily.		0.75 gm. daily.		0.5 gm. daily.		0.6 gm. daily.	
	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %
2	55	1.9	48	7.3	59	0.6	50	0.6	50	0.5	32	0.9	46	1.3	46	0.9
4	56	2.0	49	9.9	58	1.6	50	1.6	50	1.1	33	0.8	45	1.4	45	1.7
6	55	0.7	49	5.6	56	2.0	49	3.3	49	3.3	32	3.4	45	2.2	47	1.6
8	55	0.9	50	4.1	56	3.5	48	1.9	48	1.9	33	1.9	45	2.5	48	0.7
10	55	1.0	48	2.1	48	2.1	35	0.8	..	3.4	46	1.2
12	51	5.0	58	1.3	45	2.0
14	58	3.0	58	1.0
16	58	4.2	57	1.1
18	58	3.3	56	1.3
20	60	3.0	59	1.1
22	58	1.5
24	58	1.7

Iron as Above Plus Bile Pigment.

	2.2 gm. daily for 6 days.		2.0 gm. daily for 6 days.		2.6 gm. daily for 6 days.		1.3 gm. daily for 6 days.		2.0 gm. daily for 4 days.		2.8 gm. daily for 7 days.		2.5 gm. daily for 7 days.	
	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %
2	54	1.3	60	3.8	57	1.7	48	1.9	35	0.8	44	1.6	46	0.9
4	55	4.9	60	6.6	58	1.5	48	1.0	36	1.3	45	3.5	46	2.0
6	58	2.2	60	13.0	58	3.1	49	0.8	37	3.2	48	8.4	46	3.2
8	61	1.4	65	7.8	59	1.8	48	1.1	38	..	50	2.5	44	1.3
10	60	0.9	65	1.5	59	1.1	48	..	38	1.2	55	1.1	46	..
12	60	1.1
14	62	1.3

NOTE.—The red blood cell counts are not recorded. Their numbers were essentially unchanged during the observations. The average initial level was 4,000,000 per cmm. The most marked change occurred in Case 2 (*Cf.* Chart II). For the sake of brevity only the bi-daily data are recorded. The periods are consecutive. For example, the second day of the second period is 2 days after the last observation for the first period.

In the third period in which bile pigment was added, and the same dose of iron maintained, a second reticulocytosis took place with regularity, except in Case 5, which was given only 65% of the

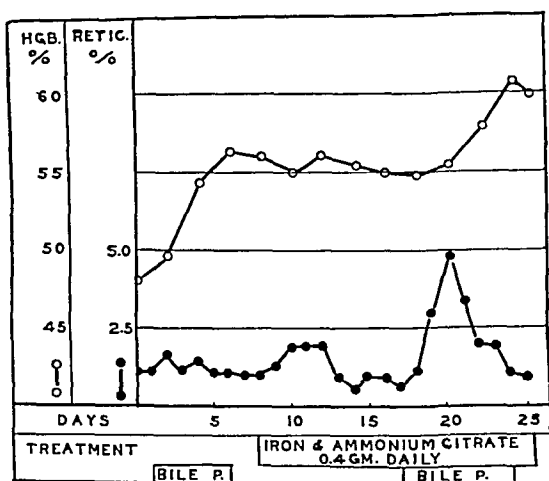


CHART I.—Hemoglobin and reticulocyte responses to the feeding of bile pigment and iron in a patient (Case 1) with chronic hypochromic anemia. This chart is scaled to illustrate clearly the effects on hemoglobin.

amount of bile pigment administered to any other case. The hemoglobin concentration increased 5% in 10 days on the average

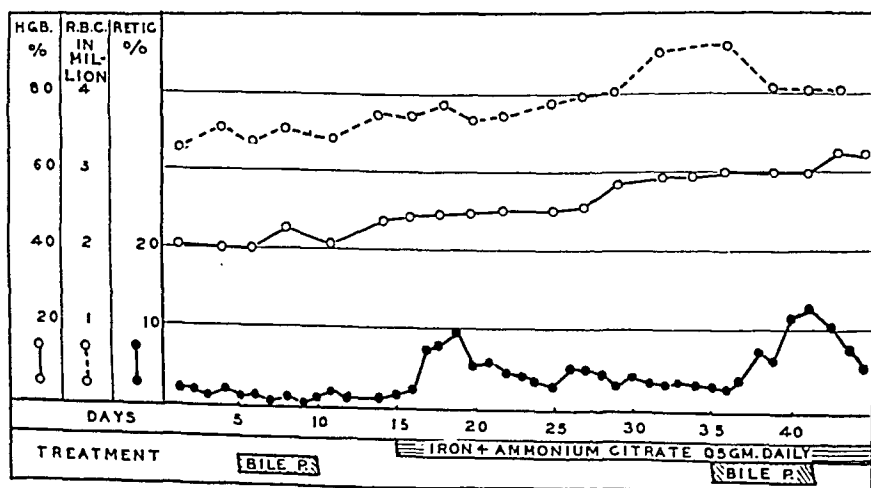


CHART II.—Red blood corpuscle, hemoglobin and reticulocyte responses to the feeding of bile pigment and iron in a patient (Case 2) with chronic hypochromic anemia.

for 5 cases, but in the other 2 cases (Nos. 5 and 8) the hemoglobin remained constant.

In all instances after these observations had been made, 6 gm. of

iron and ammonium citrate were given daily and the hemoglobin rose rapidly. In Charts I and II there is a graphic representation of the data for 2 of the cases (Nos. 1 and 2) which permits one to observe more readily than from the table the course of events.

In Table 2 are recorded synoptic data concerning a woman with severe idiopathic hypochromic anemia and achlorhydria (Case 9)

TABLE 2.—THE EFFECT OF FEEDING BILE PIGMENT IN A CASE (No. 9) WHICH DID NOT OBTAIN A NORMAL HEMOGLOBIN LEVEL WHEN TREATED FOR MONTHS WITH 6 GRAMS OF IRON AND AMMONIUM CITRATE DAILY. (Synoptic Data.)

Duration.	Hemoglobin per cent.	R. B. C. millions per cmm.	Therapy daily.
Anemic 15 years . . .	15	2.0	None.
After 3 months . . .	70	4.0	Iron.
For 7 months . . .	68-73	3.7-4.0	Iron.
For 4 months . . .	71-73	3.8-4.0	Iron + 4 gm. Vegex.
After 2 days . . .	71	3.9	Iron + 1 gm. bile pigment.
After 4 days . . .	76	4.0	Same.
After 8 days . . .	76	3.8	Same.
After 10 days . . .	80	4.2	Same.
After 12 days . . .	81	3.9	Same.
After 16 days . . .	85	4.2	Same.
After 15 days . . .	78	4.0	Iron.
After 30 days . . .	76	4.4	Iron.
After 130 days . . .	74	4.3	Iron.
After 30 days . . .	81	4.3	Iron + 1 gm. bile pigment.
After 65 days . . .	73	4.0	Iron.

who had been unable to regain a normal hemoglobin level in spite of large doses of iron. This patient, a 62-year-old widow, had been anemic for 15 years. For a long time her diet had contained little animal food, except milk and butter, and only small amounts of puréed vegetables and fruit. She suffered also from dysphagia and, although this symptom decreased greatly in severity as the hemoglobin concentration increased from 15 to 70% with iron therapy, it prevented her from being willing to take a well-balanced diet. Thus, not only while under treatment for 22 months but for years previously, her diet had been deficient in various ways. Throughout the observations she took 6 gm. of iron and ammonium citrate daily. In the 11 months before bile pigment was given, the constancy of her hemoglobin concentration, about 70%, was remarkable. The rise to 85% in 16 days, when 1 gm. daily of the bile pigment preparation was added, thus seems significant. On discontinuing pigment for 4 months the hemoglobin slowly fell to 74%. Upon resuming the bile pigment again for a month the hemoglobin rose to 81% and fell once more in about 2 months to 73% with iron alone.

This patient was also given a concentrate of vitamin B (Vegex) 4 gm. a day for 4 months to see if it could affect her hemoglobin, but it did not do so.

Discussion. The changes in the percentage figures for reticulocytes recorded with the data synopsised in Table 1 may appear unimpressive to persons who are not acquainted with reticulocyte responses in hypochromic anemia. One should recognize that a 2% increase of reticulocytes in a red blood cell count of 4,000,000 per cmm. represents a total increment of 80,000 such cells per cmm., and that under the strict conditions of the experiments, the changes which occurred are of significant magnitude. A considerable regularity of the responses and a similarity of the patterns of response to bile pigment with and without iron in the different cases, indicate that coincidence or chance are not the cause of the blood changes observed. When bile pigment alone was fed, the increase of hemoglobin concentration, although slight, occurred without appreciable change in the number of reticulocytes or red blood cells. This suggests a special focus of effect, that the pigment was absorbed and was used in the construction of hemoglobin, as McMaster and Elman⁹ and Zih¹⁰ contend took place in their animal experiments.

The data presented do not indicate the extent of hemoglobin rise with protracted feeding of bile pigment alone. There is evidence at hand that in such cases hemoglobin will increase no more than the 8 patients showed, when pigment feeding is continued beyond about 10 days.

The suboptimal daily amounts of iron were given so that any effect on blood formation of adding bile pigment could be demonstrated by the course taken by the reticulocytes. If optimal daily doses of iron are given continuously, no further response of the reticulocytes occurs after the initial reaction subsides. It has been shown, however, that if a suboptimal quantity of potent material is given daily, and no reaction or a suboptimal reticulocyte response occurs, and that if then a second reaction takes place when material is added, the substance causing the second response is more potent than the first. If the second response is greater than the first, the potency of the material responsible for this reaction is greater than the material first tested.²⁸ The data recorded in Table 1 and Charts I and II, indicate the occurrence of a second reticulocyte reaction when bile pigment was added to daily suboptimal (0.5 gm.) doses of iron and ammonium citrate. Indeed, sometimes (Cases 2 and 7) this response was as great as that usually expected with optimal doses of iron and ammonium citrate for the given hemoglobin and red-cell level, as determined by Minot and Heath.²⁹ Differences in response could depend upon the anatomical and functional state of the gastrointestinal tract and hemopoietic organs of the given patient's body. In anemia in man, seldom will these factors be identical, as may occur in experimental animals.

The second reticulocyte reaction occurred a trifle earlier and more abruptly than after the response to 0.5 gm. iron and ammonium citrate alone. This also happens when a suboptimal amount of iron is replaced by an optimal dose. It is believed, therefore, that the bile pigment facilitated either iron absorption or utilization.

We have as yet not determined whether hemoglobin regeneration with bile pigment and small doses of iron will continue to the normal level at essentially the same rate, as occurred in some of the cases in a 10-day period.

Speculation on how bile pigment increases the effect of iron is interesting but will not be discussed. Many factors must be considered, such as the composition and state of the gastro-intestinal contents, the transfer of the material across its membranes, the intermediary agents of iron and hemoglobin metabolism.

There are several factors which may enter into the etiology of chronic hypochromic anemia. Justly, Robscheit-Robbins³⁰ has criticized the confusion arising out of failure to distinguish between nutritional anemias and blood-loss anemias; but in adult human cases one dare not be dogmatic about the exact condition in a given case. For instance, the patient with chronic blood loss usually develops a poor appetite and finally a dietary lack. Achlorhydria may hinder iron absorption or utilization. Menorrhagia and pregnancy also may intensify anemia in a woman who has had a faulty diet for years.

Such conditions may explain why man may respond and why Whipple's dogs^{4,5} did not respond by increase of hemoglobin to pigments rich in hemopyrrol groups. The dogs with chronic blood loss were in good nutritional states, whereas the patient with hypochromic anemia whose diet characteristically is high in concentrated carbohydrate food and low in protein may need the factors supplied in the control "salmon bread" diet given to Whipple's dogs.

The observations we have recorded are regarded mostly as of physiologic interest because adequate amounts of iron alone alleviate hypochromic anemia in many patients. It is, of course, important for all individuals to have a proper diet. If the patient with hypochromic anemia persistently has a faulty diet, although iron can cause great improvement, the body may be deficient in other factors needed to make hemoglobin. It is suggested that such a condition occurred in the patient (Case 9) who could not obtain a normal hemoglobin level with large doses of iron. The prompt rise of hemoglobin following the feeding of bile pigment after a trial period of 1 year with iron cannot be considered fortuitous, especially when the same event took place a second time. Other cases of this sort should be observed, and determinations made as to whether bile pigment or other pigment substances sometimes may not be of therapeutic value.

Summary. Nine selected patients with chronic hypochromic anemia were studied to determine whether bile pigment could assist in hemoglobin production.

Concentrated bile pigment alone caused not a reticulocyte response but an increase of hemoglobin, about 7% in 10 days. This indicates that in certain anemic patients bile pigment can be absorbed from the gastro-intestinal tract for building hemoglobin.

After a reticulocyte response occurred to a suboptimal dose of iron, bile pigment was fed directly with the same dose of iron, and there followed a second reticulocyte response. The second response was sometimes of greater magnitude than the first. This indicates that bile pigment in some unknown manner can facilitate either iron absorption or utilization.

One patient who could not obtain in 14 months a normal hemoglobin level with large daily doses of iron promptly increased her hemoglobin concentration when bile pigment was fed in addition to iron.

It is suggested that in certain cases of hypochromic anemia there may be a deficiency of a useful material that is contained in bile pigment in addition to iron deficiency.

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NOTE ON INEFFECTIVE USE OF THEELIN IN A CASE OF HEMOPHILIA.

By LOUIS L. TUREEN, M.D.,
ASSISTANT VISITING PHYSICIAN, JEWISH HOSPITAL,
ST. LOUIS, MISSOURI.

(From the Medical Service of the Jewish Hospital.)

THE object in the treatment in hemophilia is twofold—to secure hemostasis during hemorrhage and to render the patient less susceptible to bleeding at all times. That there are numerous methods of treatment, renders all suspect. Various characteristics of the disease contribute to the difficulties of evaluation. As the patient becomes older, the tendency to bleed decreases. There is also a constantly changing tendency of a hemophiliac to bleed, and coagulation time tests made at different times may range from a normal clotting time to one which is markedly delayed. These changes may be abrupt and marked without apparent reason. It has been impossible, however, through therapeutic measures available to us, to lower the hemophiliac's clotting time, and to keep it low. The Spanish preparation, "nateina," for instance (containing vitamins A, B, C and D, with calcium phosphate and lactose), though in widespread favor in Europe at present, is not recommended by more recent studies.¹

There has always been an attempt to link the sex-limited nature of this disease with some peculiarities in the sex glands or hormones. This offered a basis for study of the therapeutic value of the female sex hormone. In 1904, Grand and Heyter² administered female sex gland by mouth. Ten years later, Schlossman³ repeated their attempts, all of which yielded unsatisfactory results. More recently, Birch^{4, 5} studied the excretion of female sex hormone in the urine of hemophiliacs and hemophilia conductors. In normal male urine, minute quantities of female sex hormone is present. In hemophilic urine, no trace of this hormone could be found. With these facts as a basis, she transplanted whole ovary into the abdominal wall of a hemophilic boy and reported that he was free from bleeding for the entire period of observation (5 months). Subsequently she has resorted to the injection of female sex hormone, with apparently good results. During the past year, several reports in the literature speak favorably of this method.^{6, 7} Mills⁸ states that biweekly subcutaneous injections of 1 cc. theelin lowers the coagulation time of hemophilic blood. Larger doses, or less frequent injections, are of less favorable value.

For the past several months we have had an opportunity to study the effect of theelin on the bleeding tendencies of a hemophiliac. In addition to the clinical observations on the frequency, duration

and severity of bleeding, we followed the effect of treatment on the coagulation time. We felt that it was important to secure a lowering of the coagulation time, which would be persistent, before we could pronounce the treatment a therapeutic success. But it is necessary, in adhering to this criterion, to remember that hemophilic blood varies in its degree of coagulability spontaneously. Hence, observations must be made over long periods of time before results can be called conclusive.

Case Abstract. The patient, at present aged 26, first came under observation in 1926 with the history of repeated bleeding in childhood. His maternal uncle is a known bleeder, but no other history of hemophilia is available. During the 7 years of observation he has had numerous severe hemorrhages, many of spontaneous origin, many others following trauma. Hemorrhages have been most often into the gastro-intestinal tract, and into the left elbow and right shoulder joints. He has required numerous transfusions, and at times has been critically sick from exsanguination. From November, 1931, to November, 1932, he had 4 attacks of bleeding into the right shoulder joint. Bleeding, swelling, pain and limitation of motion during each attack lasted from 10 to 14 days. It was toward the end of an attack of hemarthrosis in October, 1932, that theelin therapy was begun. After the second dose of 1 cc., given on successive days, the bleeding stopped promptly. Since this was about 10 days after the onset of his illness, the usual duration of previous attacks, we were inclined to consider the circumstances of treatment and result as coincidental. On November 19, 1932, pain, swelling and the usual sequelæ appeared in the right shoulder. He received 4 daily injections of 1 cc. theelin intramuscularly from November 21 to 23. After the second injection, 4 days after onset, the pain was almost gone, and he was able to move his arm. By November 23, he was over this attack, in less than $\frac{1}{2}$ of his usual period of disability.

We planned, after the elapse of a sufficiently long period of time, so that the effects of the hormone would not interfere with our observations, to make clotting time determinations, institute theelin administration and study the effect of various doses on the coagulation time and on the prothrombin time. In a symptom-free period, December 6, the results of the blood studies were as follows: Red blood cells, 4,750,000; white blood cells, 7500; hemoglobin, 70% (Sahli); fragility normal; bleeding time, 3 min.; clotting time (Howell's method), 38 min.; prothrombin time, 32 min.; clot retraction time, within 12 hr. The only abnormal findings in these tests were prolonged coagulation and prothrombin time, the normal values of which are within 10 min.

Four daily injections of 1 cc. each were given, beginning December 6. Three days after the last injection, clotting time was 30 min.; prothrombin time, 7 min. Accordingly, confident that we had secured some results, we prescribed the oral preparation of female sex hormone, theelol, 1 capsule daily. The patient continued well until December 31, when he noticed headache, dizziness and sleepy spells, which in the past had accompanied bleeding. Coagulation time now was 40 min; red blood cells, 3,690,000; hemoglobin, 45% (Sahli), with considerable occult blood in the stool. He went to bed and received a daily injection of theelin for 4 days, the last one being given on January 3, 1933. On January 5, he felt much better, and the stool had a normal appearance. On January 6, coagulation time was 12 min.; prothrombin time, 18 min.; 1 cc. of theelin was also injected. Five days later the coagulation time was still 12 min. The dose was repeated, and after another interval, this time of a week, coagulation time

had increased to 31 min., prothrombin time to over 50 min. Another dose of 1 cc. was administered on this day, January 18. On January 23, the clotting time was 23 min., prothrombin time 50 min.

A series of 4 daily injections was begun on January 26. The clotting time changed from 23 min. to 17 after the 3d injection. Prothrombin time remained at about 1 hour. Three days after the last of this series of injections, clotting time was 24 min.

A second series of injections, this time 2 cc. daily for 4 doses, was begun on February 1. The clotting time remained virtually unchanged. Prothrombin time fluctuated markedly, but inconsistently during the period of treatment and not in consonance with the coagulation time.

The dose subsequently was reduced to 2 cc. every other day. This series began on February 6 and continued through February 20, for a total dosage of 16 cc. During this time the coagulation time fluctuated between 15 and 25 min. The prothrombin time varied from 18 to 25 min. On February 21, bleeding began in the right shoulder. On February 23, coagulation time had risen to 34 min., prothrombin time to 48 min. On this date, a daily injection of 1 cc. of theelin was begun. On February 24, the coagulation time was 30 min. On February 25, the pain in the shoulder was disappearing, the patient was again able to raise his arm. The coagulation time was 22 min. On February 27, the patient was quite well; coagulation time was 24 min., prothrombin time 30 min.

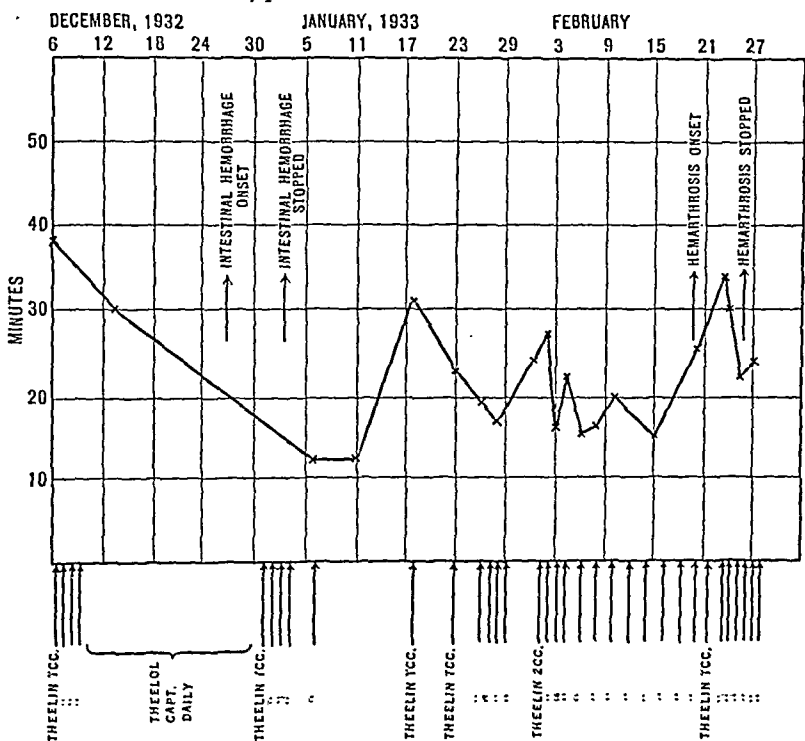


CHART I.—Curve showing effect of theelin upon coagulation time.

The accompanying chart is a summary of the treatment and the curve of the coagulation time. Although in the earlier days of observation, the clotting time seemed to decrease after the administration of theelin, and the bleeding stopped shortly after the insti-

tution of theelin treatment, twice during the course of treatment the patient developed spontaneous hemorrhages, once from the intestines and once into the shoulder joint. The coagulation time fluctuated markedly during January and February regardless of the dosage of theelin given. At no time were we able to bring the coagulation time down to a normal level, nor were we able to make any definite decrease in coagulation time, a persistent condition. Since cessation of regular theelin administration, the patient had an attack of hemarthrosis in April and a severe attack of gastrointestinal bleeding in May. After 4 daily injections of theelin the hemarthrosis stopped. However, no clinical effect was obtained with theelin during his attack of intestinal hemorrhage.

Summary. Attempts to render a hemophilic individual less susceptible to bleeding by the use of the theelin, injected intramuscularly, or administered by mouth, have failed. We have been unable to observe a constant lowering of the coagulation time as a result of this treatment, nor has the coagulation time been reduced to a normal level during the period of observation. If theelin therapy is an effective remedy, we have as yet not learned the proper dosage and interval of administration.

I am indebted to Dr. Llewellyn Sale for the opportunity to study this case.

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ABDOMINAL DISEASE SIMULATING CORONARY OCCLUSION.

BY PAUL S. BARKER, M.D.,

ASSOCIATE PROFESSOR OF INTERNAL MEDICINE

FRANK N. WILSON, M.D.,

PROFESSOR OF MEDICINE,

AND

FREDERICK A. COLLIER, M.D.,

PROFESSOR OF SURGERY,

ANN ARBOR, MICH.

(From the Departments of Internal Medicine and Surgery, University of Michigan Medical School, and the University Hospital.)

BEFORE coronary occlusion was described as a clinical entity,¹ cases of acute myocardial infarction were frequently misdiagnosed cholelithiasis, perforated peptic ulcer, or acute indigestion. Shortly after the clinical features of this condition were described, however,

a number of articles appeared in the literature reporting cases which at first appeared to be acute upper abdominal disease, but which ultimately proved to be acute coronary occlusion.²⁻⁷ The differential diagnosis of coronary artery disease and upper abdominal disease has been adequately discussed.^{3, 5-7}

More recently the knowledge of coronary occlusion has become so widespread that it is very frequently diagnosed. This diagnosis is usually made correctly, but occasionally erroneously. The result is that one now encounters cases of upper abdominal disease which have been erroneously diagnosed angina pectoris or coronary occlusion. In 1925 Robey⁸ reported 2 cases of gall bladder disease in which some of the symptoms, especially precordial or substernal pain, suggested angina pectoris, and also 2 cases in which both gall bladder disease and coronary disease were present. He also discussed the differential diagnosis. In 1932 Brown⁹ discussed atypical and referred pain due to visceral disease and pointed out that coronary disease may simulate upper abdominal disease. He also emphasized that cardiac symptoms may predominate in unsuspected gall bladder disease, and that treatment of the gall bladder condition may result in complete relief from all symptoms.

In view of the relative lack of emphasis upon this phase of the subject, it seems desirable to report 4 cases, 2 of cholelithiasis and 1 of perforated gastric ulcer in which the clinical findings were very strongly suggestive of coronary occlusion, and 1 of cholelithiasis and coronary disease, entirely relieved of all symptoms following cholecystectomy, possibly because coronary occlusion occurred during or soon after the operation.

Case Reports. CASE 1.—A retired merchant, aged 74 years, was examined, December 16, 1932, at the request of his home physician who had made a diagnosis of angina pectoris. This diagnosis was apparently based upon attacks of pain high in the epigastrium or beneath the lower sternum, occurring in an elderly man with arteriosclerotic changes and mild diabetes.

The first of these attacks occurred in November, 1931. There was severe pain high in the epigastrium accompanied by vomiting, lasting 3 hr., and relieved promptly by a hypodermic injection. The pain did not radiate. On the following day the patient felt quite well. There was no fever or jaundice.

A second attack occurred on November 17, 1932, $\frac{1}{2}$ hr. after a heavy meal. There was very severe pain high in the epigastrium, accompanied by vomiting and lasting $2\frac{1}{2}$ hr. The pain did not radiate. There was no fever or jaundice, but the patient remained in bed for 1 week. Since then he has felt weak and worn out. He has had no pain upon exertion and only slight shortness of breath.

The examination showed the patient's general condition to be remarkably good. The heart was normal in size, its rate and rhythm were normal. The heart sounds were faint, and there were no murmurs. The blood pressure was 130/80, and the brachial arteries were not thickened. The lungs were emphysematous, but there were no râles. The abdomen was negative; there was no tenderness and the liver and spleen were not enlarged. There was no edema of the extremities.

The blood count and hemoglobin were normal. The urine was normal, with the exception of a moderate amount of sugar. The electrocardiogram showed moderate left axis deviation with normal *T* waves, and was not suggestive of coronary occlusion. Roentgen ray examination showed no abnormality of the heart, but the aorta was somewhat elongated and tortuous, and its base slightly widened. Gastro-intestinal Roentgen ray studies revealed no abnormality of the stomach or duodenum. Cholecystograms after ingestion of the gall bladder dye resulted in non-visualization of the gall bladder, but also revealed a large, solitary, stratified gall stone.

The patient's symptoms were undoubtedly due to gall bladder disease. There was no evidence of heart disease. The diagnosis of angina pectoris, however, had been made and treatment for this had been instituted.

CASE 2.—A physician, aged 51, was examined, November 17, 1931. A provisional diagnosis of coronary artery disease had been made. The patient had had 7 attacks of pain in the epigastrium and precordial region. The first 5 were alike. The pain was confined to the epigastrium and was somewhat rhythmic. It bore no relation to exercise or food, excepting that all attacks occurred in the evenings of days when he felt very much exhausted. These attacks were not very severe; they lasted only 2 hr. and the patient felt quite well after the attacks. There was no nausea or jaundice.

The last 2 attacks began in the same way, but instead of relief after 2 hr., a very severe pain developed in the midprecordium, steady and not radiating, not relieved by morphin and relieved for a few minutes only by amyl nitrite. During 1 attack the blood pressure was 110 systolic, and the patient was covered with perspiration. There was no nausea, jaundice or fever. On the days following the severe attacks the patient felt quite well and was able to see his patients as usual.

The examination showed the patient to be moderately obese. The heart was normal in size; its rate and rhythm were normal. There were no murmurs. The blood pressure was 135/95. The lungs were clear. The liver and spleen were not enlarged. There was no edema.

The electrocardiogram showed slight left axis deviation, with normal *T* waves. It was not suggestive of coronary occlusion. Roentgen ray studies revealed no abnormality of the heart, lungs or stomach, but there was moderate spasm of the pylorus, the duodenal bulb was displaced somewhat posteriorly, and the gall bladder was not visualized after ingestion of the gall bladder dye. No gall stones were detected.

These findings suggested very strongly that the patient's symptoms were due to disease of the gall bladder and not of the heart.

On December 14, 1931, the patient wrote that further Roentgen ray studies had revealed spasm of the pylorus and non-visualization of the gall bladder after ingestion of the dye. He had had no further attacks.

On May 10, 1932, the home physician reported that the patient had been operated upon. The gall bladder was enlarged, its wall thickened and it contained many stones. The patient died of peritonitis following the operation.

In this case the symptoms were so strongly suggestive of coronary artery disease, particularly the transient relief from the precordial pain following the inhalation of amyl nitrite, that a provisional diagnosis of this condition was made. Further studies, however, revealed no evidence of disease of the heart, but did reveal evidence of gall bladder disease which must have been responsible for the patient's symptoms. The amyl nitrite may have relieved the pain by relaxing spasm of the pylorus or in the biliary tract.

CASE 3.—A manufacturer, aged 63, was admitted to the surgical service as an emergency at 12.30 A.M., December 10, 1930, complaining of very severe, steady pain in the midepigastrium. The pain began suddenly

3 hr. previously. It was constant, not associated with nausea or vomiting, and did not radiate. For 3 or 4 years previously he had experienced occasional cramping abdominal pains, accompanied by eructations of gas and occurring at irregular intervals after meals. He stated that his pulse had always been slow, and that he had been warned by a physician, who had examined him about 6 months previously, to restrict his activities and to avoid strenuous exertion because of elevated blood pressure and a heart condition, but he gave no history of symptoms suggesting previous heart disease.

The patient was an asthenic, elderly male who appeared acutely ill. He was ashen gray, but without apparent dyspnea or cyanosis. The oral temperature was 95° F., the pulse 52 and the respirations 16. The heart was normal in size, its rhythm regular. A definite to-and-fro pericardial friction rub was heard over the midprecordium. The heart sounds were weak. There were no signs of a valve lesion. The brachial arteries were thickened and tortuous. The blood pressure was 170/83. Throughout the upper half of the abdomen there was pronounced tenderness and muscle spasm. There was no palpable mass and the liver and spleen were not felt. The liver dullness was not obliterated, and there were no signs of ascites. The lungs were clear. There were no signs of congestive cardiac failure. The pupils and the deep tendon reflexes were normal. There was a leukocytosis of 11,650 and the urine was normal.

The surgical diagnosis was perforated peptic ulcer. The history of previous hypertension, however, the slow pulse and the obvious arteriosclerosis and, most of all, the pericardial friction sound, made it necessary to consider seriously the possibility of coronary occlusion. An electrocardiogram was taken; it showed rather flat *T* waves, much smaller than the *T* waves of an electrocardiogram taken 6 months previously, which was available for comparison. There were also occasional extrasystoles. Otherwise the curve was not abnormal, it revealed nothing definitely diagnostic of myocardial infarction. With considerable doubt regarding the diagnosis still remaining, it seemed justifiable to take the patient to the Roentgen ray room. There fluoroscopy revealed a small amount of air beneath the diaphragm, under the heart shadow, and just to the right of the gas bubble of the stomach. A film was made which confirmed this finding. The diagnosis of perforated peptic ulcer could now be made with confidence.

At operation a perforation in the anterior wall of the stomach, about 3 cm. above the pylorus, was closed and a posterior gastroenterostomy was done. Recovery was uneventful. The patient sat up on the 12th postoperative day, was soon walking and was discharged on the 20th day after operation. There were no cardiac symptoms.

Reëxamination on June 3, 1931, revealed no evidence of cardiac abnormality. The blood pressure was 140/90. In May, 1933, the patient returned to the hospital because of hematemesis. It was found that the bleeding was from a duodenal ulcer. Examination at that time again showed no evidence of cardiac abnormality. The blood pressure was 110/70 after the hemorrhage. An electrocardiogram was normal. The *T* waves were larger than those of December 10, 1930, but there were none of the changes which might suggest previous myocardial infarction.¹⁰ The patient made a good recovery.

In this case a perforated gastric ulcer was accompanied by many findings suggestive of coronary occlusion, including a pericardial friction rub and slight, but definite changes in the *T* waves of the electrocardiogram. Rather complete studies at the time, however, gave conclusive evidence of perforated peptic ulcer, and this was confirmed at operation. Subsequent observations have ruled out coronary occlusion. The manner in which the pericardial friction rub was produced remains obscure.

CASE 4.—A factory foreman, aged 54, was first examined, November 13, 1931. He complained of vomiting, epigastric pain and shortness of breath. The vomiting began 2 years previously and gradually increased in frequency until it occurred 3 or 4 times daily. It usually occurred shortly after meals, and, as a rule, only small amounts were vomited. Slight nausea and eructation of gas often preceded the vomiting. There was no history of jaundice or abnormal stools.

The epigastric pain had likewise been present for 2 years. For a long time it occurred only upon exertion and was relieved promptly by rest, but more recently it had occurred occasionally while the patient was resting. The pain always began in the midepigastrium and radiated to the precordium, left shoulder and left arm. In the latest attacks it had also radiated to the right shoulder and right arm. During the last year shortness of breath occurred upon moderate exertion. There was no history of edema. There was a chronic, productive cough.

The patient was moderately obese. The retinal arteries showed early sclerotic changes. The lungs were somewhat emphysematous, but otherwise clear. The heart was slightly enlarged; its rate and rhythm were normal; the heart sounds were distant and there were no murmurs. The brachial and radial arteries were not thickened. The blood pressure was 120/80. There was slight tenderness in the right upper quadrant of the abdomen, but the liver was not enlarged and there were no abdominal masses. There was no jaundice and no edema. There was a stricture of the urethra.

The Kahn reaction of the blood was negative. The urine and stool were normal. The gastric analysis was normal. Roentgen ray examination of the upper gastro-intestinal tract was negative. Fluoroscopically the heart appeared broad and the base of the aorta slightly widened.

The patient was given small doses of digitalis and metaphyllin. He could not take the latter because of gastric symptoms; he also stated that he could not take nitrites because they produced headache.

Because he failed to improve he entered the hospital on December 12, 1931. The examination was as before. The urine, stool, blood and spinal fluid were normal. Cholecystograms after the oral administration of the gall bladder dye revealed faint visualization of the gall bladder with evidence of a single, large gall stone. Roentgen ray examination showed slight, generalized enlargement of the heart and broadening of the base of the aorta. An electrocardiogram, taken on December 14, 1931, was normal, with the exception of slight depression of the *T* waves attributed to digitalis. While at rest in the hospital the patient had several attacks of epigastric pain which radiated not only to both arms, but also to both legs. Some of these attacks were relieved by nitroglycerin. Amyl nitrite was tried frequently without success. The diagnoses of angina pectoris, cholecystitis and cholithiasis were made.

On December 29, 1931, a cholecystectomy was performed under avertin, nitrous oxid and ether anesthesia. There was chronic inflammation of the gall bladder wall and one large calculus. During the operation the blood pressure fell to 68/50, but within a few hours it rose to normal and remained normal thereafter. For several days after the operation the patient complained at times of pain in the abdomen and chest, but this was regarded as the usual postoperative discomfort. His general condition was good at all times, and he was allowed up on the 14th day after operation. On January 18, 1932, the 20th day after operation, a second electrocardiogram was taken. It showed changes in the *Q-R-S* and *T* deflections which were characteristic of recent coronary occlusion. The patient continued to be up and about, without any pain, vomiting or shortness of breath. Electrocardiograms taken on January 25 and 29 were similar to the curve of January 18. He left the hospital on January 29.

The patient returned, as advised, for a check-up examination on March 16, 1932. He had been entirely free from symptoms referable to his heart or gastro-intestinal tract, and examination revealed no significant abnormality of the heart. The blood pressure was 115/75. An electrocardiogram on this date, however, was quite similar to the curves of January 18, 25 and 29, 1932.

This patient had gaseous eructations, nausea and vomiting which were attributed to gall bladder disease. In addition he had epigastric pain, radiating to the shoulders and arms, and shortness of breath, both definitely related to exertion and attributed to coronary disease. Following cholecystectomy he was completely relieved of the cardiac as well as the gall bladder symptoms. While under observation he must have experienced occlusion of a small branch of a coronary artery producing a relatively small myocardial infarct. It is possible that the pain of effort was due entirely to narrowing of the coronary branch which finally became occluded, so that after the occlusion the pain no longer occurred.

Summary. It has been pointed out repeatedly that in coronary occlusion an erroneous diagnosis of upper abdominal disease may be made. But little attention has been given to the fact that in upper abdominal disease a mistaken diagnosis of coronary disease is sometimes made. In view of the popularity now enjoyed by the diagnosis of coronary occlusion, and the facility with which it is made, sometimes upon inadequate evidence, it seems desirable to emphasize the fact that upper abdominal disease may simulate coronary disease to a very striking degree.

Four illustrative cases are presented. In the first two the symptoms were caused by gall bladder disease, but erroneous diagnoses of coronary disease had been made. The third case was one in which perforation of a gastric ulcer was accompanied by many of the manifestations of acute coronary occlusion, and only rather complete studies revealed the true condition. In the fourth case both cholelithiasis and coronary disease were present, and the patient was entirely relieved of all symptoms following cholecystectomy, possibly because coronary occlusion occurred during or soon after the operation. Unless the symptoms and signs are unequivocal, the diagnosis of angina pectoris or coronary occlusion should not be made until upper abdominal disease has been excluded.

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THE INITIAL VENTRICULAR DEFLECTION OF THE ELECTROCARDIOGRAM IN CORONARY DISEASE.

By T. M. DURANT, M.D.,

INSTRUCTOR IN INTERNAL MEDICINE, UNIVERSITY OF MICHIGAN,
ANN ARBOR, MICHIGAN

(From the Department of Internal Medicine, University of Michigan Medical School.)

RECENT years have been productive of a large and varied literature dealing with the electrocardiographic diagnosis of coronary disease and coronary occlusion. A large part of the work done has had as its main object the evaluation of changes in the form of the *R-S-T* segment and *T* wave. There is no doubt that characteristic changes in the shape of these ventricular deflections are of great value in the diagnosis of recent coronary occlusion, but it is well known that they are more or less transitory.

A possible relationship between abnormalities of the initial ventricular deflections and coronary disease was first suggested by Pardee¹ who pointed out that large *Q* waves in Lead III occur very frequently in association with the anginal syndrome. As a result of his studies he came to the conclusion that the presence of a *Q* wave in Lead III had diagnostic value when this deflection is followed by an upward excursion (*R*) but no *S* wave, and is at least $\frac{1}{4}$ as large as the largest *Q-R-S* deflection in any lead. Pardee attached no significance to large *Q* waves in Lead III when definite right axis deviation was present or when the initial deflections in Lead III resembled the letter *M* or the letter *W* in shape. In a group of curves meeting these qualifications he found 63 per cent to be associated with the anginal syndrome.

The diagnostic criteria established by Pardee have been subjected to considerable scrutiny by other investigators. The frequency of the anginal syndrome in different groups of cases satisfying the requirements stated has been reported by various observers as follows: Ziskin² 14%, Strauss and Feldman³ 16%, Edeiken and Wolferth⁴ 16%, Willius⁵ 38.3%, Ashman *et al.*⁶ 42%, Pardee¹ 63%. An analysis of the data given by these workers indicates that the electrocardiographic signs enumerated are more frequently associated with hypertension uncomplicated by angina pectoris or coronary occlusion, than with the anginal syndrome. Several investigators have pointed out that a transverse position of the heart may play an important part in the production of large *Q* deflections in Lead III.

It is evident that if the changes in the initial ventricular deflections produced by coronary disease are to become of any great diagnostic value they must be defined in a more satisfactory manner. The advantages that may be gained from the more certain differentiation of these changes from similar changes due to other causes

will be appreciated when it is realized that, unlike the characteristic but more or less temporary changes in the final ventricular deflections, they are permanent.

Recently, Wilson⁷ and his coworkers have emphasized the diagnostic value of the Q - R - S changes and their lasting character. They showed that two distinct types of abnormal Q - R - S deflections are frequently encountered in cases of coronary occlusion. The first of these is illustrated by the curves shown in Fig. 1 (A and B). Attention was drawn to the following distinctive features of this type of electrocardiogram: (1) the conspicuous and, in most instances, rather broad Q wave in Lead I; (2) the small amplitude of the R deflection in Lead I; (3) the absence of a Q wave in Leads II and III; and (4) the frequent presence of a large S wave in Leads II and III.

The second type of curve emphasized for its diagnostic value in coronary occlusion is illustrated by the tracings shown in Fig. 1 (C and D). Here the important characteristics pointed out were: (1) a conspicuous Q wave in Leads II and III, (2) the absence of Q in Lead I, and (3) the relatively small amplitude of the initial deflections in Lead II (Fig. 1, D).

These two types of abnormal initial deflections were referred to as curves of the Q_1 and Q_3 type, respectively; the former was found to be associated in most cases with infarcts involving the anterior, and the latter with infarcts involving the posterior wall of the heart.

One of the main purposes of the present study was to ascertain how frequently curves of the Q_1 and Q_3 types are encountered in cases in which there is no other reason for suspecting coronary disease. The second purpose was to determine what criteria, if any, could be used to differentiate between the Q - R - S changes due to coronary disease and similar changes due to other causes. The material utilized was obtained from the electrocardiographic files of the Heart Station of the University Hospital. Over 19,000 curves have been taken in this Station since 1923. Approximately 7000 are available for study in printed form; the remainder were not definitely abnormal and were not printed. All the printed curves were examined and those which showed abnormal Q - R - S deflections of the kinds in question were carefully studied. The corresponding case records were then analyzed, and various criteria were tested as to their value in the electrocardiographic diagnosis of coronary disease.

Electrocardiograms of the Q_3 Type. The first studies dealt with curves of the Q_3 type which conformed to the standards set up by Pardee, and, in addition, displayed in Lead II a Q wave at least 1 mm. in amplitude. It was soon found that it would be advisable to omit one of Pardee's requirements; namely, that Q_3 be followed by a summit (R) but no S deflection. The basis for this omission was the discovery that a number of cases of definite coronary occlu-

sion with large Q waves in Lead III failed to conform to this standard. Fig. 1, *D*, the electrocardiogram from a case of coronary occlusion proved by autopsy, illustrates this point. For similar

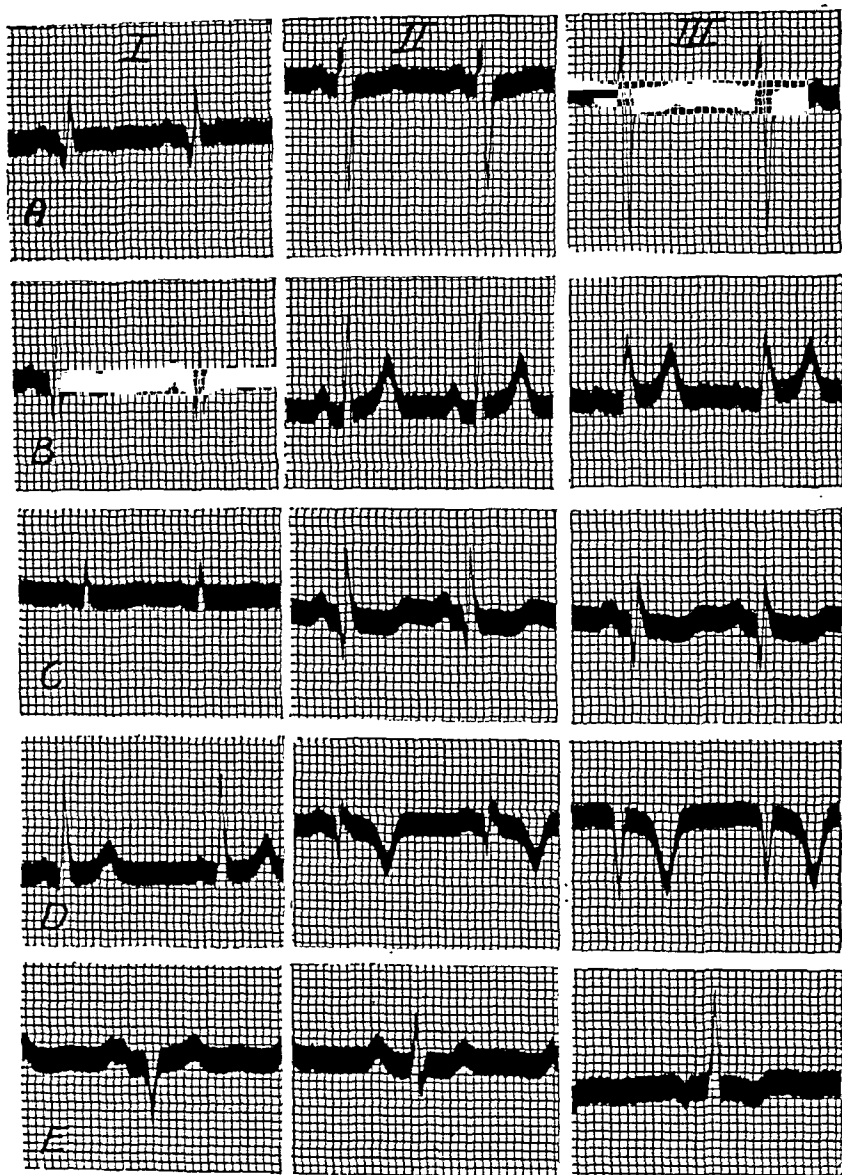


FIG. 1.—*A* and *B*, curves of the Q1 type; *C* and *D*, curves of the Q3 type; *E*, an electrocardiogram showing large Q-waves in Lead I. This curve is from a case of mitral stenosis.

reasons it was found unnecessary to eliminate curves with slight notching of the downstroke of Q3 (the *II'* complex of Pardee). Curves showing right axis deviation were excluded.

The number of electrocardiograms which met these qualifications was 96. A study of the case records revealed 31 examples of coronary occlusion and 29 cases of angina pectoris (Table 1, A). The remaining patients gave no history and showed no physical signs suggesting anginal pain or coronary occlusion.

TABLE 1.—Q3 GROUP.

Criteria.	Total cases.	Coronary disease.			No evident coronary disease.	Percentage coronary disease.
		Coronary occlusion.	Angina pectoris.	Total.		
Q3 at least 25% of largest Q-R-S deflection						
A Q2 at least 1 mm. Left axis deviation or normal axis	96	31	29	60	36	62.5
Q3 at least 50% of largest Q-R-S deflection						
B Q2 at least 25% of R2 Left axis deviation or normal axis	44	25	11	36	8	81.8
Same as under B, and in addition C T-wave inversion in Leads II and III, but not in Lead I	22	18	4	22	0	100.0

It was felt that more satisfactory results might be obtained by further modifications of the criteria used. The requirements finally selected were as follows: (1) an initial downward deflection in Lead III having an amplitude at least $\frac{1}{2}$ as great as the largest Q-R-S deflection in any lead, (2) an initial downward deflection in Lead II at least $\frac{1}{4}$ as large as R2, and (3) left axis deviation or a normal electrical axis. Clear evidence of angina pectoris or coronary occlusion was obtained in 81.8% of the 44 cases which conformed to these standards (Table 1, B). Of the 8 patients without evident coronary disease, 4 had generalized arteriosclerosis and 1 arteriosclerotic heart disease. It is possible that these patients had coronary disease which was not recognized or could not be recognized clinically. The other 3 patients with no evident coronary disease included 2 with adenomatous goiter, 1 of whom showed definite hyperthyroidism. The 3d suffered from obesity and cholecystitis, but had no demonstrable cardiac disease.

When T wave inversion in Leads II and III without inversion in Lead I was added to the requirements enumerated above, the number of cases was reduced to 22, all of which were clear examples of coronary disease (Table 1, C). It is therefore felt that when both Q-R-S changes and T wave changes of the type under consideration are found the presence of coronary disease is practically certain. In the absence of changes in the final deflections, however, a fairly

high degree of diagnostic accuracy is obtained from the *Q-R-S* variations alone.

Electrocardiograms of the Q1 Type. Curves of the *Q1* group were analyzed in a similar manner. The results are summarized in Table 2. The first step was to remove from the files all curves

TABLE 2.—*Q1* GROUP.

Criteria.	Total cases.	Coronary disease.			No evident coronary disease.	Percentage coronary disease.
		Coronary occlusion.	Angina pectoris.	Total.		
A Q1 at least 1 mm R1 less than 5 mm. Q1 at least 20% of largest R	32	13	4	17	15	53.1
B Same as under A, and in addition curves eliminated in which no R1 is present	23	13	4	17	6	73.9
C Same as under B and, in addition, inversion of T1, without inversion of T2 or T3	14	10	3	13	1	92.8

which showed the following characteristics: a *Q* wave in Lead I measuring at least 1 mm. and at least $\frac{1}{2}$ as large as the largest *R* in any lead, and an *R1* not exceeding 5 mm. in height. The incidence of coronary disease in this group of cases (Table 2, A) was relatively low because of the inclusion of a number of cases of mitral stenosis. Most of these and a few others in which there was no evident coronary disease were eliminated when all curves that failed to show a summit (*R*) following *Q1* were excluded. A curve from a case of mitral stenosis, thus eliminated, is shown in Fig. 1, *E*. The 6 cases without evident coronary disease that were not eliminated were classified as follows: mitral stenosis 2, congenital heart disease 1, arteriosclerotic heart disease with congestive failure 2, exophthalmic goiter 1. It was not found feasible in these studies to use in any way the size of the *S* wave in Leads II and III in developing diagnostic criteria, although it was found that a majority of the cases of coronary disease displayed large waves of this type.

The addition of changes in the final ventricular deflection of the *T1* type raised the incidence of coronary disease to 92.8% (Table 2, C). One case of congenital heart disease showed both *Q-R-S* and *T* wave changes and could not be excluded.

It is evident that the diagnostic value of electrocardiographic changes of the *Q1* type is considerably enhanced by the fact that those cases most often causing confusion (mitral stenosis and congenital heart disease) are as a rule readily eliminated by the clinical

findings. If the 2 cases of mitral stenosis and 1 case of congenital heart disease are left out of consideration the incidence of coronary disease under 2 B becomes 85%, a figure comparable to that obtained for curves of the Q3 type.

Incidence in Coronary Occlusion. It seemed advisable to determine the frequency of curves fulfilling the requirements described in a group of cases in which there was a definite history of coronary occlusion. Seventy-four cases were collected in which a certain diagnosis of coronary occlusion could be made from the history, from the precordial electrocardiogram, or from autopsy findings. Thirteen of these satisfied the criteria given in Table 2, B. Twenty-five curves were of the Q3 type and met the requirements given in Table 1, B. Thus 38 cases (51.3% of the total number) showed initial ventricular deflections of either the Q1 or the Q3 type, as defined in this article.

Initial ventricular variations of the kinds described are, therefore, infrequent in conditions other than coronary disease, but occur in approximately $\frac{1}{2}$ of the cases of coronary thrombosis. It is, of course, obvious that any modification of the diagnostic criteria which tends to eliminate non-coronary cases also excludes some cases of coronary disease.

Summary. Two types of *Q-R-S* deflections are characteristic of coronary disease; the Q1 type and the Q3 type. Curves of the Q1 type may be defined as those in which Q1 measures at least 1 mm. and is at least $\frac{1}{2}$ as large as the largest *R* deflection in any lead, and in which there is a definite *R* wave in Lead I, measuring less than 5 mm. in amplitude. Curves of the Q3 type may be defined as those in which Q3 is at least $\frac{1}{2}$ as large as the largest *Q-R-S* deflection in any lead, and in which Q2 is at least $\frac{1}{4}$ as large as *R2*. Curves showing right axis deviation must be eliminated.

The relatively permanent nature of these changes in the *Q-R-S* deflections in contrast to the more or less transitory changes in the *R-S-T* segment and in *T* greatly enhances their value in the recognition of coronary disease, and particularly in the diagnosis of old myocardial infarcts.

Indebtedness is acknowledged to Dr. Frank N. Wilson for the suggestions and help rendered by him in the carrying out of this study.

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ATYPICAL BUNDLE-BRANCH BLOCK WITH A FAVORABLE PROGNOSIS.

BY HENRY T. VON DEESTEN, M.D., F.A.C.P.,

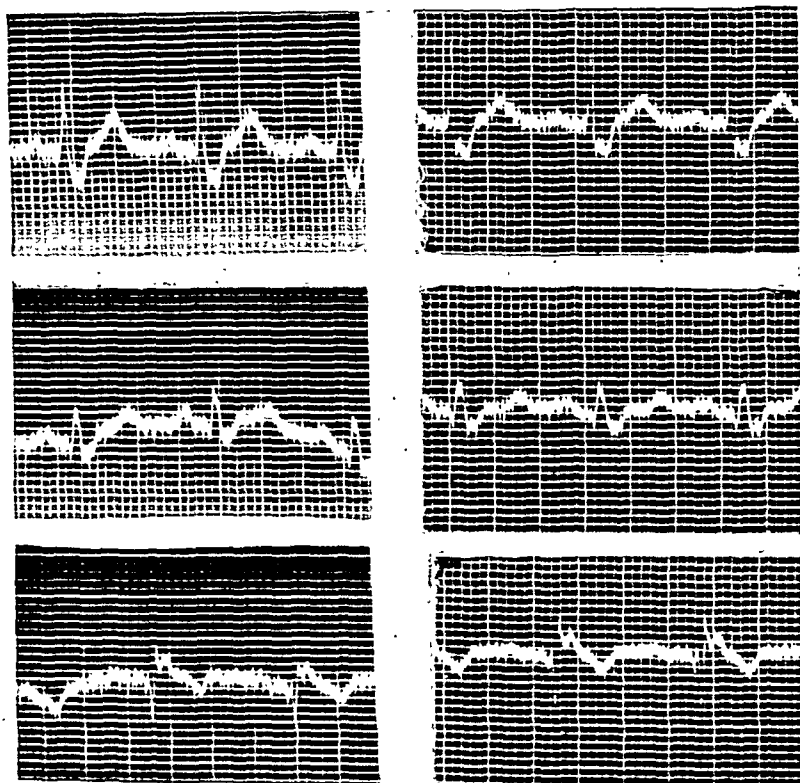
ATTENDING PHYSICIAN TO THE MEDICAL CENTER, CONSULTING PHYSICIAN TO CHRIST HOSPITAL, JERSEY CITY, N. J.; BAYONNE HOSPITAL, BAYONNE, N. J.; HUDSON COUNTY HOSPITAL, SECAUCUS, N. J.,

AND

MOSES DOLGANOS, M.D.,

PHYSICIAN TO CHRIST HOSPITAL, JERSEY CITY, N. J.; HUDSON COUNTY HOSPITAL, SECAUCUS, N. J.

The following cases illustrating a type of atypical bundle-branch block are reported because of the longevity of 2 patients and the mildness of the cardiac symptoms in all of them.



April, 1923.

September, 1930.

FIG. 1.—Case 1. Other electrocardiograms taken in the interval between the above dates show the same configuration.

Bundle-branch block generally indicates serious myocardial damage. The literature and textbooks have called attention to the poor cardiac reserve and early mortality of patients having bundle-

branch block. Graybiel and Sprague have analyzed 395 cases of bundle-branch block. Their follow-up of 308 cases showed an average duration of life of 1 year and 2 months in 223 fatal cases. The chief cause of death was cardiac failure. Eighty-five patients who are living for an average of 2 years and 11 months have a limited cardiac reserve.

The electrocardiographic records in all of the cases here reported of atypical bundle-branch block, except for minor variations, are

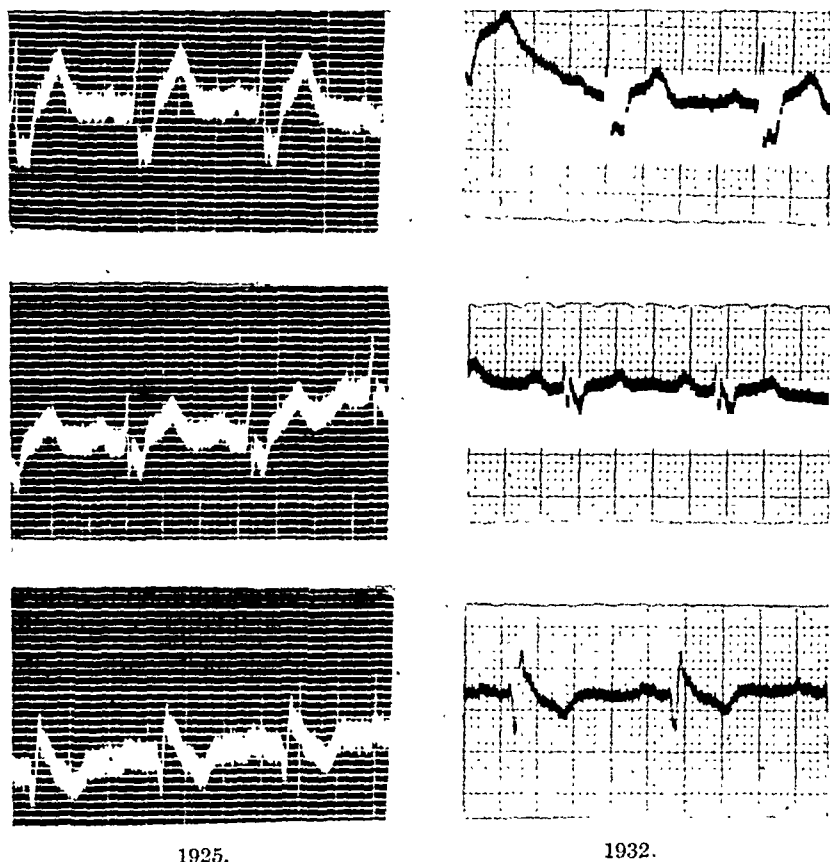
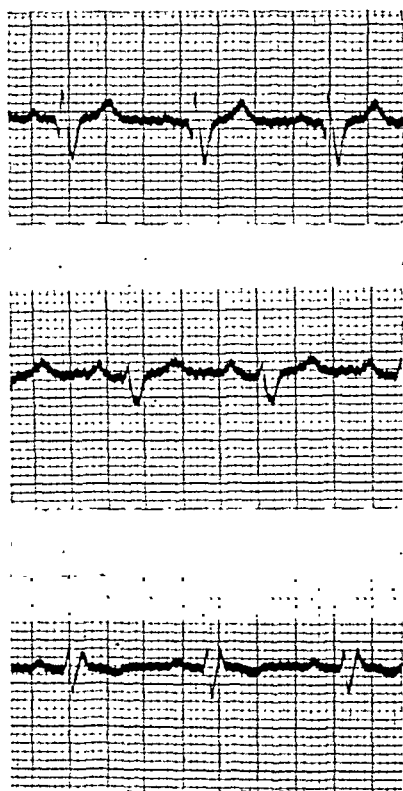


FIG. 2.—Case 2. Other electrocardiograms taken in the interval between the above dates show the same configuration.

similar. A brief description of the curves is as follows: 1, *Q-R-S* complex has a prolonged duration; 2, Lead 1, an *R* wave of moderate amplitude and short duration is followed by a prolonged notched *S* wave. The latter has a smaller amplitude than the *R* wave. 3, the *T* wave is upright in Leads 1 and 2; 4, the initial phase of the *Q-R-S* complex in Lead 3 is downward, returning quickly to above the isoelectric line where the curve is notched and prolonged. The *T* wave in Lead 3 is directed downward; 5, except for the lower

amplitude the *Q-R-S* complex in Lead 2 is similar in most curves to Lead 1. The character of the curves is confusing in regard to the localization of the lesion in the conducting system and is referred to as atypical bundle-branch block.

All of our cases of atypical bundle-branch block have occurred in males. One patient is living $11\frac{1}{2}$ years after the diagnosis was made; 1, 8 years after; 1 seen $2\frac{1}{2}$ years ago with this type of block



May, 1931.

FIG. 3.—Case 3. Other electrocardiograms taken since this date show the same type of curve.

is doing hard work; 1 recently observed in a hospital, a man aged 70, exhibiting this type of block left the institution and has not been subsequently heard from; 1 first examined $1\frac{1}{2}$ years ago has continued his occupation.

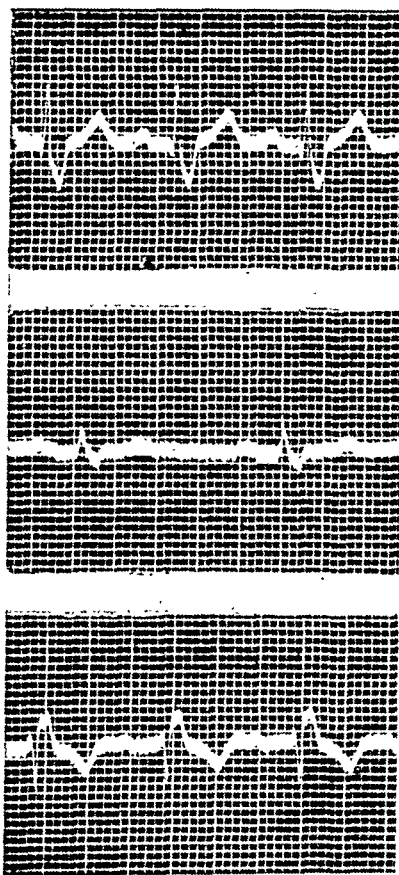
Synopsis of Case Histories. CASE 1 (Fig. 1).—H. S., aged 72, $11\frac{1}{2}$ years ago was referred to one of us on account of the symptoms of acute indigestion and slight dyspnea. His occupation necessitated much stair climbing. He discontinued this occupation and is in fairly good health at the present time. Numerous electrocardiograms, taken during this period, show the same type of curves.

CASE 2 (Fig. 2).—T. B., physician, aged 54, actively engaged in the practice of medicine; hypertensive individual. Eight years ago, on account of numerous extrasystoles, decided to have an electrocardiogram taken. Until

the present time frequent electrocardiograms show the same curves. He has not curtailed his activities.

CASE 3 (Fig. 3).—A. B., male, aged 51, was first seen in May, 1931, complaining of moderate pain in the left precordial region. He does hard physical work and has not changed his occupation since his first visit, and the electrocardiogram remains the same.

CASE 4 (Fig. 4).—B. C., aged 78, was admitted to the hospital on account of vertigo. A routine electrocardiogram showed the same type of atypical bundle-branch block curve. He had no cardiac symptoms.



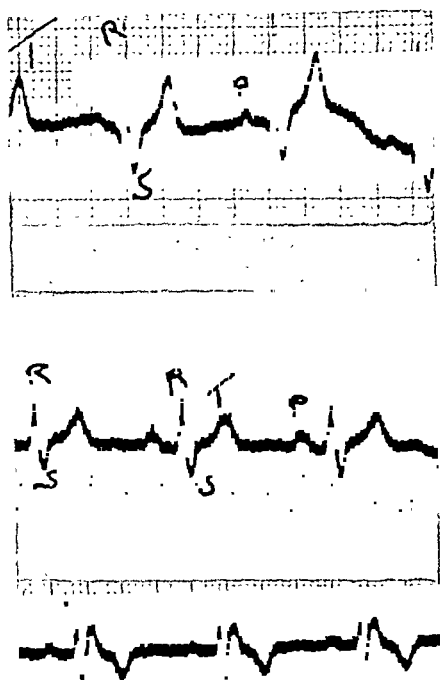
January, 1929.

FIG. 4.—Case 4. No other electrocardiogram taken on this case.

CASE 5 (Fig. 5).—M. S., aged 49, insurance collector, was referred to one of us on account of vertigo and vague epigastric distress with the request that an electrocardiogram be taken. It showed the same type of atypical bundle-branch block curve. He was very much distressed on account of the prognosis given him, based on an electrocardiogram taken previously and interpreted as one of hopeless invalidism. He continued his occupation after reassurance. A recent electrocardiogram shows the same type of atypical bundle-branch block.

Comment. Since the more frequent use of the electrocardiograph and the tendency to base prognosis on instrumental rather than on

clinical findings, misinterpretation of the graphic records of this type of atypical bundle-branch block may cause great apprehension, chronic invalidism and impairment of earning power.



May, 1932.

FIG. 5.—Case 5. Other electrocardiograms taken since this date show the same type of curve.

Summary. 1. Five cases of atypical bundle-branch block showing similar curves are presented.

2. One of these patients is alive at the end of $11\frac{1}{2}$ years, at the age of 72. Another is alive at the end of $8\frac{1}{2}$ years, at the age of 54.

3. Four have no cardiac symptoms at the present time; one we have not been able to follow.

4. Numerous electrocardiograms in 4 of these patients have remained the same through many years.

5. Hypertension is present in only 1 of these patients.

NOTE:—The Editor would like to mention in this connection another example of a healthy man (T. C. H.) aged 47 who repeatedly for the last 16 years has shown a so-called bundle-branch block without any evidence of cardiac disease or diminution of cardiac reserve. The possibility of an anomalous course of the distribution of the healthy branches and terminals of His' bundle should be considered in such cases.

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THE FREQUENCY AND SIGNIFICANCE OF RIGHT BUNDLE-BRANCH BLOCK.*

By R. H. BAYLEY, M.D.,
INSTRUCTOR, DEPARTMENT OF MEDICINE,
ANN ARBOR, MICHIGAN.

(From the Department of Internal Medicine, University of Michigan Medical School.)

For many years it has been the universal opinion that myocardial disease interrupts one branch of the His bundle very much more often than the other. This opinion is based upon the relative frequency of the 2 types of electrocardiograms currently attributed to bundle-branch block. According to different observers, the common type right branch block of the older terminology is seen 5 to 10 times as often as the less common. It is evident that our ideas respecting the incidence of bundle-branch lesions of both kinds depend upon the criteria generally accepted for the classification of electrocardiograms with broad $Q-R-S$ deflections. Observations made in this laboratory suggest that both varieties of branch block are considerably more common than is at present supposed.

It has been shown¹ that precordial leads taken by pairing an exploring electrode placed over the precordium with an indifferent electrode placed on the left leg, or with a central terminal connected through equal and sufficiently large resistances to the 3 extremity electrodes, are of great value in locating the conduction defect in intraventricular and particularly in bundle-branch block. These precordial leads are so taken that relative negativity of the exploring electrode produces an upward deflection. The majority of precordial electrocardiograms show a sudden and pronounced upward excursion at some time during the $Q-R-S$ interval. This *chief upstroke* represents a sudden large negative variation in the potential of the exploring electrode, and signals the arrival of the excitation process at the epicardial surface of the subjacent portions of the ventricular wall. In bundle-branch block the upstroke is early when the exploring electrode is placed over the contralateral and late when it is placed over the homolateral ventricle. The time of the chief upstroke is measured with reference to the first ventricular deflection in Lead I, which is taken simultaneously with each precordial lead.

In cases in which the standard electrocardiograms exhibit all the features regarded as characteristic of bundle-branch block of the less common variety, the chief upstroke is early in leads from the left side and late in leads from the right side of the precordium. Precordial curves with similar time characteristics have, however,

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been obtained in all patients tested who had standard electrocardiograms in which the ventricular complex showed a Q - R - S interval of 0.12 sec. or more and a broad S deflection in Lead I. It has, therefore, been suggested that all such electrocardiograms represent complete right bundle-branch block.²

It is the purpose of this article to present the results of an analysis of all the electrocardiograms of the kind mentioned that could be found in the files of this laboratory,* and of the case histories of the patients from whom these curves were obtained. The chief object of the study was to determine the relative frequency of right and left branch block and with what kinds of heart disease they are most often associated. It was thought that such a study might indicate the nature of the factors that determine which of the several forms, presently to be described, the ventricular complex will take when right bundle-branch block develops.

As a first step, all the electrocardiograms which showed a Q - R - S interval of 0.12 sec. or more were critically examined; 70 curves were found which were regarded as representing complete right bundle-branch block. In addition to a lengthened Q - R - S interval, all these curves showed a broad S deflection in Lead I. None were included in which the value of the chief initial deflection failed to exceed 5 mm. in at least 1 lead.

The curves selected fell naturally into 4 more or less distinct groups:

GROUP 1.—The 14 curves in this group showed all the features generally accepted as necessary for the interpretation of bundle-branch block of the less common type (Fig. 1, A , B , C). In Lead I the chief initial deflection of these curves is a broad downward excursion, S , which is preceded by a smaller upward movement, R . T_1 is upright. In Lead III, the chief initial deflection is a broad, notched, upward excursion, R , which is preceded by smaller dip, Q . T_3 is inverted.

GROUP 2.—Twenty-three curves were similar to those of the preceding group in all respects except that in Lead I the amplitude of the R spike was greater than that of the S deflection. (Fig. 1, D .)

GROUP 3.—In this group, 28 curves were placed because of the character of the initial deflection in Lead III. In these curves the most conspicuous Q - R - S deflection in this lead is a slender, deep, inverted spike, usually preceded by a small and invariably followed by a broad summit (Fig. 2, A , B). The amplitude of this last deflection is less than that of the inverted spike. In Lead I the ventricular complexes are similar in all respects to those of the curves placed in Group 2.

GROUP 4.—Only 5 curves were placed in this group. They were separated from those of the preceding groups chiefly because they lacked a broad upward movement in Lead III. In this lead the

* Heart Station, University Hospital, Ann Arbor, Michigan.

initial deflection is a small summit, which is followed as in Group 3 by a deep inverted spike (Fig. 2, *C, D*). At its apex the inverted spike is narrow, but the ascending limb, after rising sharply, usually shows a pronounced notch, beyond which its ascent is gradual (Fig. 2, *D*). The base of the inverted spike is, therefore, greatly broadened. In some instances this broad upward movement in

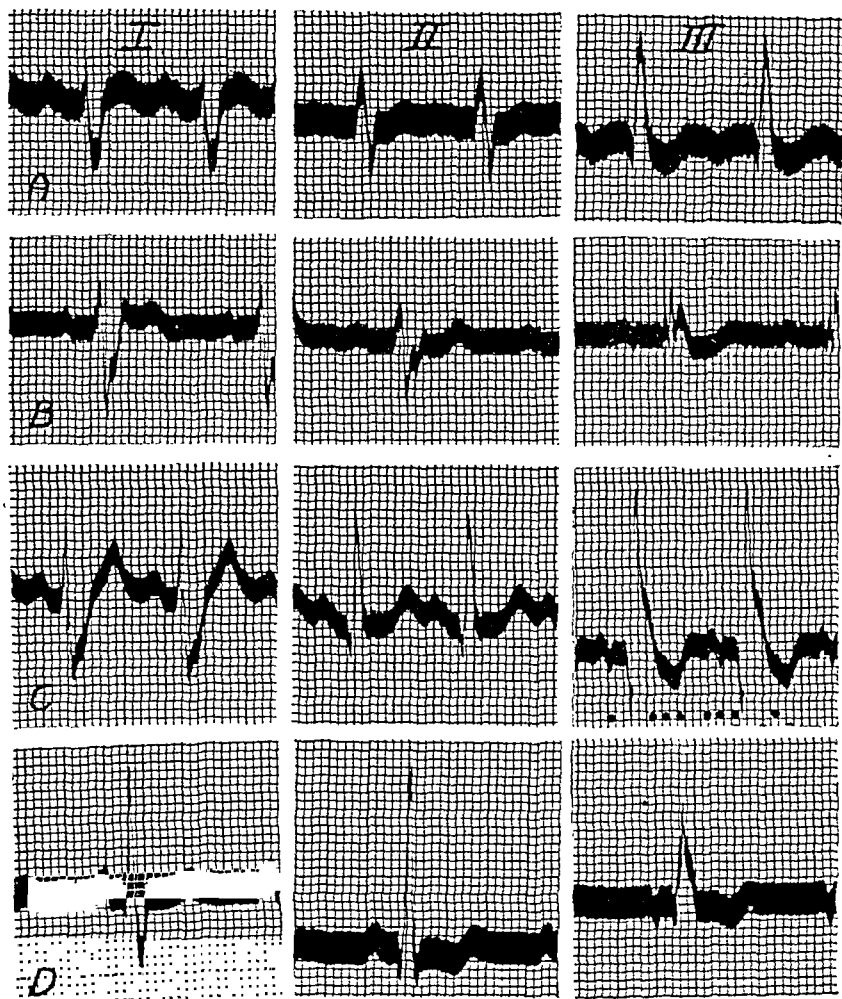


FIG. 1.—*A, B, and C*, electrocardiograms of the type placed in Group 1. *D*, an electrocardiogram of the type placed in Group 2.

Lead III is absent, and the ascending limb returns quickly to the baseline and does not leave it during the remainder of the *Q-R-S* interval (Fig. 2, *C*). The distinguishing feature of these curves is the absence of a broad upstroke at the end of the *Q-R-S* interval in Lead III. In Lead I the *Q-R-S* deflections are similar to those which characterize Groups 2 and 3, except that *R* is usually taller

and broader and *S* less conspicuous. T_3 is usually upright. Some of the curves of the last 2 groups (3 and 4) might easily be confused with those that represent left bundle-branch block, from which they may be differentiated by the presence of a conspicuous and broad *S* in Lead I.

An analysis of the case records of the patients from whom these 70 curves were obtained, showed that no single etiologic factor or

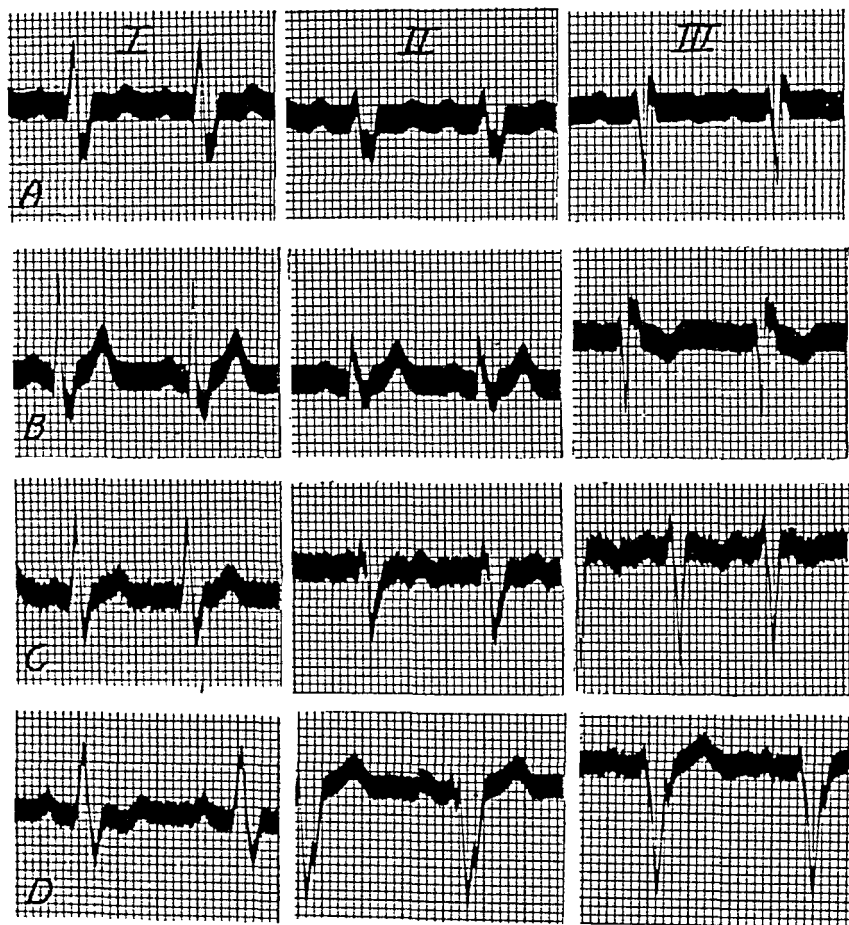


FIG. 2.—*A* and *B*, electrocardiograms of the type placed in Group 3. *C* and *D*, electrocardiograms of the type placed in Group 4.

kind of heart disease was responsible for the whole of any one of the 4 groups. It was anticipated that patients with rheumatic heart disease and mitral stenosis uncomplicated by aortic insufficiency, and, therefore, with right or at least with no left ventricular preponderance, would, on developing right bundle-branch block, display curves of the kind placed in Group 1 or 2. In 5 of these cases with these specifications, the curves were of the anticipated varie-

ties. In 1 case of congenital heart disease the electrocardiogram was of the type placed in Group 2.

It was also thought that patients with right branch block and vascular hypertension of sufficient duration to have produced left ventricular preponderance would be more likely to display curves of the varieties placed in Groups 3 and 4. Only 3 of the 11 cases of this kind showed curves of the type anticipated; in the remaining 8, the curves belonged to Group 1 or 2.

The majority of 46 patients with arteriosclerotic heart disease displayed curves belonging to Group 1 or 2. Curves of this kind were also recorded in 1 case of primary nephritis and secondary hypertension, in 2 cases of syphilitic heart disease with aortic insufficiency and in 2 cases of thyroid heart disease.

These observations do not suggest that the left axis deviation displayed by the curves placed in Groups 3 and 4 is due to preponderant hypertrophy of the left ventricle. Preponderant hypertrophy of the right ventricle would not be expected to influence the initial portion of the *Q-R-S* complex in complete *right* bundle-branch block since the excitation of the right ventricle in this condition is a relatively late event, and the first part of the curve is, therefore, written by the left ventricle. It is believed that the position of the heart, infarction of the septum or free wall of the left ventricle, and preponderance of the left ventricle are the chief factors whose absence or presence, singly or in combination, accounts for the variations of the form of the initial deflections of the *Q-R-S* complex observed in right branch block.

The third purpose of this study was to gain some conception of the relative incidence of right and left bundle-branch block and find out in what kinds of heart disease these conditions most often occurred.

There were 103 curves which showed the characteristic changes of complete left bundle-branch block. All had the *Q-R-S* interval increased to 0.12 sec. or more, and the amplitude of the chief initial deflection exceeded 5 mm. in at least 1 of the 3 standard leads. Since the examination of the same material disclosed only 70 cases of complete right bundle-branch block, complete left bundle-branch block appears to be the more common in the ratio of 103 to 70.

Of the 103 patients with left branch block, 86 had records that were available for the more detailed analysis that follows. Reference to Table 1 will show that 70% of all patients with branch block of either type had arteriosclerotic heart disease. The average age of these 110 patients with arteriosclerotic heart disease at the time the conduction defect was discovered was 64 years. The vast majority were men. The heart was of normal size in at least $\frac{1}{3}$ of the cases, and on the routine physical examinations there were no objective signs of congestive heart failure in at least $\frac{2}{3}$. Many of the patients presented little or no clinical evidence of cardiovascular

disease on routine physical examination. Further reference to the table will show that lesions of the left bundle branch are more common than lesions of the right, both in arteriosclerotic and in hypertensive heart disease. The patients with hypertensive heart disease, however, almost all showed evidence of cardiovascular disease on routine physical examination and almost $\frac{1}{2}$ of them were women. The average age in the hypertensive group was 54 years. The single patient with rheumatic heart disease and left bundle-branch block had mitral stenosis with aortic insufficiency, while the 7 patients with the same kind of heart disease and right bundle-branch block had only mitral stenosis. These findings would suggest that the conduction defect is more likely to occur in the ventricle which is subjected to the greater strain.

TABLE 1.—THE RELATIVE FREQUENCY OF RIGHT AND LEFT BUNDLE-BRANCH BLOCK IN VARIOUS TYPES OF HEART DISEASE.

Etiology.	Left branch block.	Right branch block.	Per cent.
Arteriosclerotic heart disease	64	46	70.0
Hypertensive heart disease	15	11	17.8
Rheumatic heart disease	1	7	4.9
Syphilitic heart disease	4	2	3.6
Thyroid	2	2	2.5
Chronic nephritis with hypertension	1	0.6
Congenital heart disease	1	0.6
Total	86	70	100.0

The incidence of physical signs usually described as suggestive of a complete bundle-branch lesion was also noted in the 156 case records examined; the presence of a visible or palpable double apical systolic thrust was recorded only once; reduplication of the 1st or of the 2d heart sound was recorded 8 times; gallop rhythm, 13 times; there was no instance in which asynchronous systolic murmurs were detected. The presence of a bundle-branch lesion was suspected in only 1 instance before the electrocardiogram had been taken. Of the patients, 24% gave no symptoms and presented no signs of heart failure; 21% had no cardiac enlargement; and 60% had no physical signs of congestive heart failure. On the other hand, only 9% had marked cardiac enlargement. These findings indicate that the average patient with bundle-branch block shows little evidence of cardiovascular disease on routine physical examination, and one is frequently surprised when the electrocardiogram discloses a serious conduction defect. Unless an electrocardiographic examination is made more or less routinely in patients above the age of 40 years, many bundle-branch lesions may escape detection.

Conclusion. In the files of this laboratory curves of the variety ascribed to complete interruption of the left branch of the His bundle are somewhat more common than those interpreted as evi-

dence of interruption of the right branch (newer terminology). The proportion is 103 to 70. Right bundle-branch block is far more common than hitherto supposed. Seventy curves of the right bundle-branch type fell naturally into 4 more or less distinct groups, differentiated one from another by the character of the Q-R-S deflections. Only a small percentage of the patients with complete right bundle-branch block displayed diphasic ventricular complexes of the less common variety. The position of the heart, infarction of the interventricular septum or free wall of the left ventricle and preponderance of the left ventricle are probably the chief factors, whose absence or presence, singly or in combination, accounts for the variation in the form of the initial deflections encountered in curves from patients with complete right bundle-branch block. Both right and left branch block are considerably more common in arteriosclerotic heart disease than in the other etiologic types. There is often little or no evidence of cardiovascular disease on routine physical examination. When patients with rheumatic heart disease and mitral stenosis develop bundle-branch block, the conduction defect is almost invariably on the right side. In the case records examined, only 1 instance was encountered in which the routine physical examination suggested bundle-branch block.

Thanks are given to Dr. Frank N. Wilson for his constant guidance and suggestions during the course of this study.

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PERSISTENT FUNCTIONAL ALBUMINURIA.

ANALYSIS OF 58 CASES WITH RESULTS OF THYROID AND CALCIUM MEDICATION.

BY NELSON J. BURDEN, M.D.,

PHYSICIAN, STUDENT HEALTH SERVICE, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA.

THERE is at present no satisfactory explanation for so-called functional albuminuria. Physicians engaged in the medical care of adolescents are frequently confronted with this form of urinary disturbance and are often at a loss to know the proper disposition of the patient. While the abnormality does not appear to be harmful, the question of treatment, especially restriction of activities, frequently arises. Aside from this we are, of course, interested in the etiology of functional albuminuria and, if possible, removal of the cause. The patient is not so easily disposed of as Fishberg¹ would have us believe, by simply establishing a diagnosis and then

dismissing him by saying no treatment is indicated. To many physicians, especially those engaged in general practice, the finding of albumin in the urine means kidney disease, calling for removal of foci of infection, restriction of physical activities, lessened exposure, dieting in the form of protein restriction and iron medication. Every year we receive several letters from family physicians requesting that boys be excused from all forms of exercise because of the finding of albumin in their urine. In some instances even a fall in the scholastic standing of the student has been attributed to albuminuria, which supposedly affected his health.

Functional albuminuria was described as early as 1886 by Pavy,² who suggested poor posture as the cause of this abnormality. Since that time many other theories have been advanced to explain functional albuminuria and various names have been applied to the abnormality, the most recent being "benign albuminuria" (Fishberg).¹ Until we have definite proof of the cause and significance of these unexplained albuminurias, it would be better to call them idiopathic or essential albuminurias. It is probably true that albuminuria detectable by ordinary clinical tests is never functional. While the ultimate prognosis³ in these cases appears to be almost invariably good, and about $\frac{1}{3}$ of the cases clear up after the age of 30, nevertheless, there may have been some temporary or underlying kidney damage. After a discussion of the extrarenal factors in albuminuria, Volhard⁴ concluded that every albuminuria must be attributed to damage of the kidney epithelium. When we recall that chronic nephritis is the result of repeated injuries to the kidneys, and that the urine between acute exacerbations may be normal, we get a glimpse of possible harm in this apparently innocent disturbance.

An analysis⁵ of the records of 3642 male students at this university showed that 26% had occasional and 6.4% persistent albuminuria, with no other evidence of kidney disease. Even if we concede those with only an occasional albuminuria to the class of individuals who during a physical examination show a slight elevation of blood pressure, an increased pulse rate, and perhaps a slight glycosuria without hyperglycemia, we still have the cases of persistent albuminuria to account for. The first group may be excused on the basis of vasomotor instability, but we cannot help wondering whether these repeated "functional" disturbances may not in time lead to organic changes in the kidneys, heart and bloodvessels.

Analysis of Cases. The present report is based on further analysis of 58 cases of persistent albuminuria and the application of 2 theories on the etiology of the abnormality. The ages of the students varied between 17 and 28. The heat and acetic acid test for albuminuria was used and the amount recorded ranged from a faint trace (1+) to a heavy cloud (4+). Occasional hyalin and granular casts were found in 20.3% of the cases. As to body weight, 17% of the

students were more than 10% overweight, while 21.2% were more than 10% underweight. The tonsils had been removed in 78.7% of the patients, while in 20.8% the tonsils were present and pronounced infected by the otolaryngologist. Only 1 student had a non-vital tooth, negative for abscess by Roentgen ray report. The blood pressure, taken in all of the cases, was never over 150 systolic. Only 5.1% had systolic pressures between 140 and 150. The average pulse pressure for the entire group was 50; 2% had a pulse rate over 90 and in 20% the rate was less than 70. Only 1 student had a moderate lordosis of the lumbar spine. Complete blood counts were done on all, with a normal result in every case. There were no hemoglobin estimations below 80%. All of the students were Mantoux-tested, and those with a positive reaction had chest roentgenograms, but no case of active tuberculosis was found. The past medical histories of the students were apparently irrelevant, as no disease or other abnormality occurred with unusual frequency. Scarlet fever had occurred in 20.7% and 13.3% of the students admitted "frequent" head colds, with about the same figures for a control⁶ group. The family histories of the students showed cardio-renal disease in 1 of the parents in 12% of the cases, more than double that found in a control⁶ group.

An orthostatic response to the albuminuria was present in 58.6% of the functional albuminuria patients. This was determined by having the patient completely empty his bladder immediately before retiring and then as soon as he awoke the next morning voiding a specimen while still in the recumbent position. In the cases with orthostatic albuminuria this early morning specimen was free of albumin.

The phenolsulphonephthalein test intravenously was done in 25 of the subjects, and the average total output of dye in 2 hr. was 70%. In 24% of the cases the total output for 2 hr. was between 80 and 88%. In 56% it was over 70% and in no instance was the total output less than 50%. The Mosenthal test on this same group showed that the night urine exceeded the day urine in 12.1% of the cases. In 30.3% the specific gravities of the day specimens varied more than 10 points, and in 50% it varied more than 7. In no instance was the variation in specific gravity less than 5 points.

Functional Albuminuria and Nephrosis. Since all attempts to prove these unexplained albuminurias as due to renal damage have thus far failed, it was thought that perhaps we were dealing with a temporary derangement of metabolism similar to Epstein's nephrosis (diabetes albuminuricus). It is now fairly well agreed that there exists a "nephrotic syndrome" characterized by general edema, marked albuminuria and lowered basal metabolism. This may be present in the absence of other evidence of kidney diseases (hypertension, arterial changes and impaired renal function), as shown by normal kidney excretion tests and blood values. The edema occur-

ring in nephrosis is believed due to the condition of hypoproteinemia resulting from loss of large amounts of protein as albumin in the urine.⁶ The albumin excreted in functional albuminuria is usually small and probably rarely approaches the minimal amount of 1 gm. of protein per liter a day, which appears necessary to cause hypoproteinemia.⁷

A basal metabolism was done on all of our cases, and it was found that 80.9% had a minus rate (average, -7). A basal metabolic rate below -15 was present in 21.4% of the albuminurics as compared with 14% in 100 control basal metabolism determinations in male students of the same age group without albuminuria. Ten of the functional albuminuria patients with lowered basal metabolisms were given thyroid extract in doses of gr. ss, gradually increased to gr. i, 3 times a day for 2 weeks. In none of the cases was there any apparent change in the occurrence or in the amount of albumin.

Calcium in Functional Albuminuria. If we dismiss abnormal protein metabolism as the cause of functional albuminuria, and admit that albuminuria is not ordinarily due to foreign toxic proteins in the blood stream,⁸ and that the plasma proteins of patients with albuminuria show no increased diffusibility,⁹ one may attribute functional albuminuria to some form of renal injury, however mild and transient. Cushny¹⁰ attributes albuminuria to alterations in the glomerular capsule which allows the passage of plasma proteins. It is well known that albuminuria can readily be produced by interrupting the blood supply of the kidney by compression of the artery or vein, or of the ureter which leads to pressure on the vein. The albuminuria in these experiments is due to asphyxia, which produces temporary damage resulting in increased permeability of the glomerular capsule¹⁰ or of the glomerular capillaries.¹¹ It has also been demonstrated that vasoconstriction produced experimentally by adrenalin injections or increased adrenalin secretion causes albuminuria.¹² According to these views, functional albuminuria is probably the result of some form of pathologic physiology of the kidney, most likely an increased permeability of the glomerular tuft. It is well known that calcium diminishes the permeability of cell membranes and that this effect is not dependent upon the entrance of the salt into the interior of the cell.¹³ Patients with nephritis, as well as patients with nephrosis, often show a hypocalcemia.

Normal blood values for urea, uric acid, creatinin, sugar and alkali reserve have been reported¹⁴ in cases of functional albuminuria, but no reference is made to the serum calcium. The normal serum calcium values for adults is generally set between 9 and 11.5 mg. and for infants 10 to 11.5 mg.¹⁵ Serum calcium determinations in normal boys,¹⁶ between the ages of 8 and 20 years, were found to range from 7.6 to 12.5 mg.

The blood serum calcium was determined on 10 of the students with persistent functional albuminuria. The blood was obtained by venoclysis before breakfast and the amount of serum calcium present was determined according to the method of Clark and Collip. In the 10 cases examined, the serum calcium ranged between 10.5 and 12.2 mg. In 5 of the determinations the values were over 11.5 mg., *i. e.*, on the high side of normal.

The fact that the total blood calcium is normal or even high in cases of persistent albuminuria does not necessarily mean that the albuminuria may not be due to a deficiency of one of the calcium fractions. It has been shown¹⁷ that calcium is present in the serum in at least 4 forms, 2 of which are diffusible and 2 non-diffusible. Of the diffusible calcium, about $\frac{2}{3}$ is in the form of an "adsorbable calcium-phosphorus complex" and the remainder contains the calcium. The "protein-bound" fraction of the blood calcium is of the non-diffusible form and the amount varies roughly with the total protein concentration, and so it is this form of calcium which is reduced in cases of nephritis and of nephrosis, and accounts for low values for total serum calcium in these conditions. On the other hand, certain diseases as adult human rickets, which show a normal or even high serum calcium, may have low values for the diffusible fraction, especially in the "adsorbable calcium-phosphorus complex."¹⁷ Despite the finding of normal total serum calcium in cases of persistent functional albuminuria, it was thought advisable to try the effects of calcium ingestion. Calcium gluconate, in dram doses 4 times a day for 2 weeks, was given to 16 of the students with persistent functional albuminuria. The result was that in 5 (31.2%) of the cases there was no change in the condition, while 6 (37.5%) showed a definite decrease in the amount of albumin excreted, and in the remaining 5 (31.2%) there was a total disappearance of the albuminuria. In other words, 68.7% of the cases showed improvement or total disappearance of the albuminuria.

Further examination of the 5 "recovered" cases 1 year after their last dose of calcium showed that 4 of them still remained free of albuminuria.

Conclusions. 1. Nothing was found in the past medical histories or in the physical examinations of 56 otherwise healthy male students with persistent functional albuminuria to account for the urinary abnormality. The kidney function as determined by the phenol-sulphonephthalein and Mosenthal tests was normal.

2. Cardiorenal disease in the parents of students with functional albuminuria was more than twice as frequent as in the parents of students showing no such abnormality.

3. A tendency to low basal metabolism readings was found in 80.9%, but in the 10 cases tested with moderate doses of thyroid extract there was no improvement in the albuminuria.

4. The blood serum calciums were normal in 10 students with persistent functional albuminuria, although calcium medication had a favorable influence on the albuminuria in 11 of 16 cases tried.

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THE RELATION OF NEGATIVE PRESSURE IN THE EPIDURAL SPACE TO POSTPUNCTURE HEADACHE.

BY WILLIAM M. SHEPPE, M.D.,
WHEELING, W. VA.

(From the Medical Division of the Wheeling Clinic.)

THE examination of the spinal fluid has come to be recognized as an essential part of many general medical examinations. Its value is even more important when dealing with individuals known to have syphilis. It is well established that invasion of the central nervous system may begin soon after the appearance of the primary lesion and that physical examination and blood Wassermann tests are often insufficient to detect the presence of neurosyphilis. Many cases of syphilis (I refer particularly to the cutaneous manifestations of the disease) are discharged from treatment without knowledge of the spinal-fluid findings. I feel that many physicians are deterred from the use of this valuable diagnostic procedure for fear of the prolonged and disagreeable symptoms which may and often do follow lumbar puncture. Nelson¹ states that about 20% of the

lumbar punctures at the Mayo Clinic produce definite postpuncture reactions. Stokes⁸ reports an incidence of 15 to 25% of headache produced in hospital patients. These figures seem very high when the test is conducted on patients who are hospitalized and at rest for 24 hours or more following puncture. It is obvious that such a high percentage of disagreeable reactions deters the physician's hand and tends to place the procedure in disrepute among his clientele. If the above figures may be accepted as typical of the incidence of postpuncture headaches in hospital patients, one wonders what the incidence is in ambulant patients.

The question of the substitution of cisternal puncture for lumbar puncture is as yet unsettled. It is my opinion that it cannot be recommended as a routine procedure and that patients have an innate fear of being "stuck in the head." I am sure that in the hands of a competent neurologist cisternal puncture is relatively safe; I am equally sure that it is unsafe in the hands of many men who must of necessity carry out examinations of the spinal fluid.

It is highly desirable and important that the technique of lumbar puncture should be brought to a point whereby it may be performed on ambulant patients with very little pain to the patient or the development of distressing or deleterious sequelæ. This paper outlines certain factors which tend to produce postpuncture headaches and describes a technique which has rendered feasible the performance of lumbar puncture on ambulant patients.

Causes of Postpuncture Headaches. It has been well established that the removal of spinal fluid in ordinary amounts and at ordinary speed does not result in postpuncture headache. The amount of fluid removed has very little to do with the degree of the reaction. Headache, vertigo and nausea are apparently due to persistent postpuncture leakage of spinal fluid through the needle hole in the dura. That such leakage does take place has been demonstrated by Ayer,⁷ who injected lampblack into the cistern of cats. The lampblack was found at necropsy to be lying beneath the cervical muscles. Further proof for this view is adduced by Nelson,⁴ who performed repeated lumbar punctures during and after postpuncture headaches. Careful estimations of pressure were made at the beginning and at the completion of the withdrawal of fluid. If headache developed, a third pressure measurement was taken during the course of the headache. The spinal-fluid pressures during the headache were found to be consistently lower than the pressure following completion of the original puncture. This may be taken as evidence of a further fall of pressure following withdrawal of the needle. It is obvious therefore that headache probably is to be avoided by preventing postpuncture leakage of spinal fluid from the dura. While such leakage is minimized by the supine position, it is evident that it is not eliminated. Let us examine a few of the factors which determine postpuncture leakage:

1. *The Size of the Needle.* Greene's^{1,2} studies (1923) conclusively demonstrated that persistent leakage from the dura is due directly to the amount of trauma to the spinal dura sac. He further demonstrated that the rate of flow from the dural sac was directly proportional to the size of the hole made by the needle.

2. *Shape of Point.* Greene was able to demonstrate by microscopic examination of the dura that much greater trauma was produced in the membrane by the use of a needle with a blunt cutting point than by a needle of the same caliber with a sharp tapering point. The elastic and fibrous lamellæ of the dura run longitudinally and almost parallel. The pointed needle simply separates these fibers instead of cutting them and there is much earlier closure of such a wound. The above observations therefore suggest the use of a needle which should not be larger than 22- to 25-gauge.

The needle which I employ at present is a 22-gauge, $3\frac{1}{2}$ inches in length, with a sharp, tapering point. The point resembles that of a cambric needle, and the opening is below the apex.*

The objection may be raised that a small needle is more liable to break. Exactly the contrary is true. A needle of this size may be bent at right angles, straightened and still be serviceable. Dr. Greene has very kindly presented me with a needle which he frequently tied in a knot and untied prior to performing a puncture. This needle has been used for the performance of about 500 lumbar punctures and was still entirely usable. Further objection may be raised that the flow from such a needle is too slow. This is easily obviated by attaching a 10-cc. syringe to the needle and aspirating the required amount of fluid. Many textbooks contain grave warnings against the aspiration of spinal fluid. Those of have had experience with the making of encephalograms know that this anxiety is ill founded. It is also true that in case of the development of symptoms suggestive of medullary pressure, the most satisfactory treatment would be replacement of the spinal fluid which had been withdrawn. If this is under control in the syringe this may be readily and quickly done.

An additional advantage of the small needle is that it is flexible enough to move freely with the dura. Any accidental movement of the head produces an up-and-down movement of the dural sac in the bony canal. If a rigid needle is used, being fixed by two points of attachment (skin and interspinous ligament) it is unable to bend. As a result, the dura saws over the needle with each movement of the head with resultant enlarging of the needle opening and greater opportunity for postpuncture leakage. It is needless to say, of course, that the small needle produces much less trauma to the skin and ligament and is therefore less painful to the patient. If the needle is falsely directed in the first attempt, additional punctures

* Such a needle may be obtained from Becton Dickinson & Co., Rutherford, N. J. (No. 460 LNG).

may be made without undue discomfort to the patient. If the patient is extremely muscular, an 18-gauge needle may be passed through the skin and interspinous ligaments following the application of novocain. The small needle will then readily follow the track of the 18-gauge needle.

Results of Use of Proper Needle. All observations recorded in this discussion were made on ambulant patients examined by the Division of Medicine or of Neurology at the Wheeling Clinic. These candidates for puncture report to us at 9 A.M. They remain at the Clinic in bed until 4 P.M. At this time they are allowed to return home, employing various means of transportation which vary from a long walk to a trip by railroad, bus or automobile. The distance which individual patients travel varies from a few blocks to 50 miles. Obviously, such patients cannot follow the dictum of Stokes.⁸ "After the patient lies down following the puncture, he should not sit up again for at least 24 and preferably 48 hr." The adoption of the needle as described above reduced the incidence of postpuncture headaches in our patients from approximately 10 to 5%. However, if lumbar puncture were to be made as often as indicated on ambulant patients, it became imperative to reduce the incidence of headache still lower.

Observations Leading to Further Reduction in Postpuncture Headaches. 1. The appearance of a drop of spinal fluid on the skin following the withdrawal of the needle.

2. In punctures in which some difficulty is experienced in entering the dural sac, or if for any reason the stylet was withdrawn from the needle before the dural sac was entered, we often noted a slight but distinct hissing sound as if there were a sudden inrush of air into the needle.

3. We have observed that if the needle is slowly withdrawn following successful puncture that the drop of fluid in the hub of the needle was sometimes aspirated inward. This seemed to occur just after the needle point emerged from the dura.

4. Strangely enough, the punctures which were performed with the greatest ease were apparently the ones which lead most frequently to postpuncture headaches. In other words, punctures which were accomplished with one simple advancement of the needle, resulted more frequently in postpuncture reaction.

We were at a loss to explain or to correlate these isolated observations until the publication of the excellent work of Heldt and Maloney.³ These workers, having noted the same phenomena, concluded that a condition of negative pressure existed in the epidural space, somewhat comparable to the negative pressure existing in the pleural spaces. The development of such a negative pressure was believed to be due to late embryonic and early fetal extension of the vertebral column. The more rapid growth of the bony struc-

tures produces a caudal elongation of the vertebral canal away from the conus terminale of the slower growing, encephalad fixed cord. They found this negative pressure to vary from -1 to -18 mm. of mercury. We have constructed a manometer similar to their model and have been able to confirm their findings in certain individuals (14 patients in this series). The amount of negative pressure in the epidural space varies greatly and probably is not present in all patients. We have no explanation for this apparent variation. Two statements may be made in regard to the measurement of this pressure. If the needle is advanced too far and impinges on the dura without puncturing it, a false negative pressure will be registered as the epidural space is increased by the forward pressure on the dura. Second, we have not been able to demonstrate negative pressure in individuals who have had multiple lumbar punctures. It is probable that the degree of negative pressure in the epidural space is affected by, (1) the amount of spinal fluid present, *i. e.*, the expansion or contraction of the dural sac; (2) filling and emptying of the epidural veins with change of posture. If the presence of a negative pressure in the epidural space may be assumed as seems justified by the observations of Heldt and Maloney, and our own observations, it is obvious that the opportunity for leakage to occur depends upon the balance of the pressure existing in the subdural and epidural spaces at the needle opening. Negative epidural pressure would tend to aspirate fluid through the dural opening no matter how small this opening may be and such aspiration might be expected to continue until an equalization of pressure was established. So long as such leakage continues, postpuncture headache might be expected, from small but steady withdrawal of fluid from the subdural space. It should be pointed out also that the withdrawal of fluid from the spina dural sac decreases the space occupied by the spinal membranes, thereby increasing the volume of the epidural space with a resulting increase in negative pressure.

Prevention of Postpuncture Headaches Based Upon the Above Observations. Nelson⁴ advises the plugging of the dural opening with a strand of catgut inserted by a very ingenious instrument which he has devised. This has also been attempted by Heldt and Maloney⁵ with success so far as the obviation of headache is concerned. However; the use of the catgut has resulted in rather severe reactions marked by rise in temperature and disagreeable leg pains.

Remembering our observation that the easy punctures produce the most headaches, we concluded that the repeated withdrawal of the stylet during the more difficult punctures allowed the outside air to pass through the needle to the epidural space, thereby raising the pressure in that region at least temporarily to atmospheric figures. We have therefore made it a practice to halt the needle in the epidural space during each puncture and allow it to remain *in*

situ with the stylet removed. The puncture is then continued in the usual way. On completion of the puncture the stylet is not replaced but the needle is withdrawn again into the epidural space. It is allowed to remain there for 30 sec. before being pulled out through the ligaments. It is our belief that the air thus allowed to enter the epidural space serves temporarily at least, as a cushion against the leakage of fluid from the dural sac.

Since we have adopted: (1) The use of a needle not greater than 22-gauge with a sharp tapered point; (2) the practice of slow withdrawal of the needle with full time allowance for the entry of air to the subdural space, we have been able almost completely to obviate the complication of severe postpuncture headache. In the last 100 examinations done on ambulant patients, 3 have complained of slight headaches the day following puncture. These were not severe and did not necessitate the patient giving up his or her usual daily activities. We consider this a reduction of the incidence of postpuncture headaches to less than 3%. The morbidity in this series is so slight that it may be disregarded.

Summary. 1. The more frequent examination of the spinal fluid, especially in suspected syphilis, is advocated.

2. A review of the literature, combined with our own confirmatory observations, strongly suggests that continued leakage of spinal fluid from the dural sac is the predominant cause of postpuncture headache. This continued leakage may be obviated by: *a*, use of needle not larger than 22-gauge with a sharp tapering point; *b*, the elimination of the negative epidural pressure, shown by manometric readings to exist in at least some individuals. This is accomplished by allowing an inflow of air through the needle while the point rests in the epidural space.

3. The observance of the precautions mentioned above has resulted in marked reduction in the incidence of postpuncture headache in our series (from 10% to 3%). This has been accomplished despite the fact that puncture is performed regularly on ambulant patients.

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THE EFFECT OF NON-SEDATIVE DRUGS AND OTHER MEASURES IN MIGRAINE.*

WITH ESPECIAL REFERENCE TO ERGOTAMIN TARTRATE.

BY SAMUEL BROCK, M.D.,

ASSOCIATE PROFESSOR OF NEUROLOGY, UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL SCHOOL,

MARY O'SULLIVAN, M.D.,

RESIDENT, NEUROLOGICAL SERVICE, BELLEVUE HOSPITAL,

AND

DAVID YOUNG, M.D.,

RESIDENT, NEUROLOGICAL SERVICE, BELLEVUE HOSPITAL,
NEW YORK CITY.

(From the Neurological Service of Bellevue Hospital, Dr. Foster Kennedy, Director.)

THE excellent review of Riley¹ has so completely covered the subject of migraine that an extensive survey is unnecessary at this time. Like the convulsive state, migraine is a symptom complex due to a number of causes. Allergic reactions, hormonal imbalance, water retention and instability of innervation of the meningeal and cerebral vessels have been regarded as etiologic factors. At present, most students of the subject believe that a vascular spasm in the meningeal and cerebral vessels forms the pathophysiologic basis.

To evaluate the results of the drug actions to be described, it is necessary to understand the vasomotor innervation of the cerebral circulation. Direct photomicrography has demonstrated vasomotor control of the cerebral circulation (Forbes and Wolff²), and the pathway in cats and monkeys has been traced by Cobb and Finesinger³ and Chorobski and Penfield.⁴ Stimulation of the proximal end of one vagus nerve induces *bilateral cerebral vasodilatation—a parasympathetic action*, whereas *stimulation of the cervical sympathetic causes ipsilateral vasoconstriction* of pial vessels.

In the following study we have investigated the effects of non-sedative drugs and other measures in a group of individuals suffering from typical long-standing, severe and intractable migraine. The medical, neurologic, nasal and serologic examinations were entirely negative. The basal metabolic rates and roentgenograms of skull and nasal sinuses were normal. There were 19 women ranging in ages from 19 to 64 (average, 37) and 6 men from 36 to 48 (average, 42). The duration of the disease in both groups averaged 21 years. The headaches occurred from 2 to 12 times a month. Menstruation was a provocative factor in 13 of the 19 women.

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The effects of the various measures are summarized in Table 1. Hypodermic medication was used to avoid the uncertainties attending gastro-intestinal absorption.

TABLE 1.—THE RESULT OF VARIOUS MEASURES IN THE PRODUCTION AND RELIEF OF MIGRAINOUS HEADACHE.*

Measure used.	Relief.	Doubtful.	No relief.	Intensification.	Headache.	
					Produced.	Not produced.
Hyperpnea	13 (11 F) 3 (2 M)
<i>Subcutaneous injection</i>						
Follutein	4 (4 F)	11 (8 F) 2 (2 M)
Pitressin	1 (1 F)	4 (4 F)
Insulin	1 (1 F)	18 (11 F) 1 (1 M)
Histamin	5 (4 F)	3 (3 F)	4 (3 F)	5 (3 F)
Adrenalin	2 (2 F)	3 (3 F)	1 (1 F)	3 (3 F) 1 (1 M)
Ephedrin	2 (2 F)	6 (4 F)	1 (1 F)	1 (1 F)
Ergotamin }	27 (11 F)	3 (2 F)
tartrate }	7 (3 M)	2 (2 M)
Mecholin	6 (4 F)	4 (4 F)	1 (1 F) 1 (1 M)	1 (1 F)
Amniotin	2 (1 F)	15 (3 F)	1 (1 F)	3 (2 F)
Tissue Extract 568	3 (3 F)	3 (3 F)	1 (1 F)	1 (1 F)	1 (1 M)
Caffein sodium benzoate	4 (4 F)
Amyl nitrite (by inhalation)	2 (2 F)	2 (2 M)
Calcium gluconate (by intravenous injection)	2 (2 F)	3 (3 F)	1 (1 M)	3 (3 F)	1 (1 M)
			1 (1 M)

* The numbers refer to the number of experiments. F = woman; M = man.

Hyperpnea. Since migraine bears a well-known relationship to the convulsive state, it is natural that hyperpnea which induces convulsions in about 40% of epileptics should be used to provoke headache. Muck⁵ investigated 27 cases of migraine and found that the headache could be produced in those individuals who gave a positive reaction to adrenalin applied to the nasal mucous membrane.

In our series, 11 women were subjected to 13 hyperpnea tests and 2 men to 3 tests without the appearance of headache. The period of overventilation lasted 8 to 10 minutes. The patients complained of uncomfortable tingling and numbness in the extremities and showed positive Chvostek sign; 1 woman developed tetanic spasms. The adrenalin test described by Muck was not used in this series.

Follutein (or *Antuitrin S*). This preparation contains 2 of the hormones of the anterior lobe of the pituitary gland—an ovarian follicle-stimulating hormone (Prolan A) and a luteinizing hormone (Prolan B). Riley, Brickner and Kurzrock⁶ found prolان in the urine before or during a migrainous headache in 20 of 29 instances. They injected 2 cc. of follutein intramuscularly in 9 women and were able to produce a characteristic headache in 7, in 4 to 12 hours. In 1 of 2 men the injection of follutein induced a headache. We injected 1 cc. of follutein subcutaneously and produced the typical headache in 4 women, but failed 11 times in 8 other women. Follutein in 1-cc. dosage failed twice in 2 men.

Pitressin. This is a hormone derived from the posterior lobe of the pituitary gland. It has proven useful in diminishing the urinary output in cases of diabetes insipidus. Forbes and his co-workers⁷ have shown that local intravenous injections of pituitary extract and pitressin cause dilatation of the pial arteries in anesthetized animals in 65% of the cases and constriction in 19%. Pitressin is believed to promote water retention in tissues. Földes⁸ believes that migraine is due to increased water retention in meningeal and cerebral tissues.

We injected 1 cc. of pitressin in 4 women and at the same time forced fluids. No headaches resulted. In 3 of the cases increased retention of water was not actually proven.

Insulin. An attempt was made to produce the headache by the injection of insulin. In 11 women and in 1 man, 19 injections of 10 or 15 units failed to produce the headache in the fasting subject; in 1 woman a headache was induced. Apparently a state of low blood sugar is not an important cause of migraine.

Histamin. This is beta-aminazoly ethylamin. According to Sollmann,⁹ histamin causes an extensive fall of blood pressure due to capillary dilatation. It acts on the vessel wall with an effect opposite to that of adrenalin. One-half cubic centimeter of 1 to 1000 histamin phosphate was injected and its effect noted for a period of 3 hours. In 4 women it afforded no relief 5 times. In 3 women the headache was intensified. In 3 other women headaches were produced on 4 occasions; in 3 women it failed to produce headache 5 times. Since histamin is a capillary dilator, one would expect that it might help those individuals whose headaches were relieved by ergotamin tartrate, the action of which is also believed to be one of vasodilatation, dependent upon sympathetic paralysis. However, injections of ergotamin tartrate eased the headache in 1 woman on 9 different occasions, whereas in the same patient histamin failed twice to affect the headache, and the third time made it worse. Another woman was benefited on 2 occasions by ergotamin tartrate but was not relieved by histamin.

Adrenalin. Forbes, Finley and Nason¹⁰ have shown that the intravenous injection of adrenalin causes a rise in general blood

pressure and a secondary dilatation of the pial bloodvessels in cats and monkeys. When adrenalin is applied locally to the surface of the brain it induces a more or less mild vasoconstriction. In our cases, 1 cc. of a 1 to 1000 adrenalin solution was injected. In 6 women it helped twice and failed 3 times; in 1 woman the headache was intensified. In 3 women and in 1 man no headache was produced by the end of 1 hour. In 1 woman relief was obtained twice, but similar benefit also followed the injection of the vasodilator, ergotamin tartrate. In another woman, ergotamin tartrate was ineffective. In 2 other instances, ergotamin tartrate was effective, whereas adrenalin failed. The relationship of these 2 drugs will be discussed below.

Ephedrin Sulphate. In 2 women an injection of 1 cc. of ephedrin sulphate (gr. $\frac{3}{4}$) gave relief, but in 4 other women 6 headaches were unaffected. In 1 woman the headache was intensified; in another it failed to induce headache. In 1 of the women relieved by ephedrin the headache was also favorably influenced by ergotamin tartrate. However, 3 headaches in 1 woman were unaffected by ephedrin and a 4th was made worse; the same woman was completely relieved on 4 different occasions by ergotamin tartrate.

Ergotamin Tartrate (Trade Name, "Gynergen"). This is one of the alkaloids of ergot which was isolated by Stoll,¹¹ in 1918, in crystalline form. Dale¹² pointed out that there was a "specific pharmacologic antagonism" between ergotoxin and adrenalin. Ergotoxin paralyzes the sympathetic augmentor functions stimulated by adrenalin. *Ergotamin* paralyzes both the motor and inhibitory endings of the sympathetic nervous system according to Rothlin,¹³ and bears the same relationship to the sympathetic system that atropin bears to the parasympathetic.

Ergotamin tartrate has been used in the treatment of migraine for a number of years. Tzanck,¹⁴ in 1928, noted improvement in 8 subjects; 2 of 3 sufferers from status migrainosus were reported as "almost cured." Trautmann¹⁵ described favorable results in the treatment of 30 patients. Kottmann¹⁶ reported improvement in 5 patients with sympathicotonic features. He noted also that subcutaneous injection had a more intense and beneficial effect than oral administration. He stressed the involvement of the vegetative nervous system in migraine, and reëmphasized the grouping of migrainous subjects into sympathicotonic and vagotonic types. By the successful use of ergotamin tartrate, Kottmann believes that one can isolate the sympathicotonic group from other types of migraine which are unbenefited by this drug.

In this series, 11 women were benefited 27 times and 3 men, 7 times. Two women were not relieved during the course of 3 headaches and 2 men were not helped in 2 headaches. At no time was a headache made worse. Headaches once removed by this drug were always eased by it; if the drug failed on the first injection,

it was ineffective on future trials. Injection of 0.5 (0.25 mg.) to 1 (0.5 mg.) cc. of ergotamin tartrate caused the headache to disappear in 1 to 3 hours. Vomiting frequently accompanied relief. Ergotamin tartrate may be given orally in pill form in 1-mg. dosage. In our experience, subcutaneous was more effective than oral administration. At times the taking of 1 mg., 2 to 4 times a day by mouth, during the symptom-free interval lessened the frequency and severity of the attacks. In 1 of our cases in which benefit occurred, the discontinuance of the drug precipitated a very severe headache. This seemed comparable to the outbreak of convulsive seizures when phenobarbital is suddenly stopped after prolonged usage.

Acetylcholin and Mecholin. Loewi¹⁷ first demonstrated the action of the vagus hormone in 1921. He showed that vagus stimulation of a frog's heart liberated a substance which entered the perfusing solution. This perfusate was capable of stimulating a second frog's heart in a vagotonic manner. The name, "Vagus-Stoff" was given to this hormone which is the direct antithesis of the sympathetic hormone—adrenalin. The vagus hormone is acetylcholin or a very closely allied compound. Acetylcholin is very rapidly disintegrated in the body. Simonart¹⁸ isolated a more stable compound, the acetyl ester of betamethyl cholin (mecholin). Wolff¹⁹ observed dilatation of the cerebral arteries, veins and minute vessels in the cat after the intravenous injection of acetylcholin. When subcutaneously injected in man in 15-mg. dosage, mecholin produced a striking reaction, characterized by flushing, salivation, lowering of blood pressure, with rise in the pulse rate. The tachycardia seemed to be a compensatory phenomenon offsetting the low blood pressure.

In 4 women 6 headaches were relieved very promptly; in 4 other women it was ineffective 4 times. It produced headaches in a man and in a woman on 2 occasions, and once it failed to induce headache in a woman. In our most intractable case of migraine, injection of mecholin produced immediate and remarkable relief on 3 occasions after many other measures had been unsuccessfully tried. Though relief is almost immediately attained, the headache is apt to reappear after $\frac{1}{4}$ to $\frac{1}{2}$ hr. as the action of the drug wears off.

Parasympathetic (vagus) stimulation induced by mecholin has not the same effect as regards the headache as sympathetic paralysis believed to be produced by ergotamin tartrate. For we have seen instances in which mecholin failed to relieve headaches in an individual invariably relieved by ergotamin tartrate. Moreover, in a man benefited by the latter, mecholin at one time produced a headache.

Amniotin. This is the estrus-inducing or ovarian follicular hormone. Amniotin is prepared from fetal amniotic fluid. One cubic centimeter (equalling 50 rat units) was the dose used in this series.

One woman was relieved of 2 headaches, but it failed in 3 other women on 15 occasions. In 3 women it produced a headache or intensified one on 4 occasions. Since Riley, Brickner and Kurzrock⁶ demonstrated the deficiency of this hormone in the urine of women suffering from migraine, before and during the headache, one might expect its administration to have a beneficial effect in prevention. However, this has not occurred even when the hormone was given repeatedly over a number of days. Indeed, in 1 woman, 5 cc. (250 rat units) produced a headache on 1 occasion and 2 cc. (100 rat units) on another.

Tissue Extract 568. This is a pancreatic derivative which is said to contain neither histamin nor cholin in sufficient quantities to explain its physiologic action. According to Wolffe and his co-workers,²⁰ it is said to have a vasodilator effect contrary to that of adrenalin. It is standardized in terms of units (10 units to 1 cc.). One unit of tissue extract is said to neutralize the pressor effect of 1/1000 mg. of adrenalin. It was administered in doses of 3 cc. subcutaneously (30 units), with the following results: In 3 women, 3 headaches were relieved; in 3 other women there were 3 failures; once it did not produce a headache in a man, but on another occasion it provoked a headache in a woman. Once a headache was intensified in a woman. In 1 woman unrelieved by mecholin, relief was gotten from tissue extract though the headache reappeared the next day. In a man in whom mecholin produced a headache, tissue extract failed to induce one.

Caffein Sodium Benzoate. It has been known that there is no increase in intracranial pressure during a migrainous headache, hence no benefit may be anticipated from the use of drugs which decrease intracranial pressure, such as caffeine. Four women and 2 men were unrelieved of their headaches by the subcutaneous administration of this drug, in dosage of gr. viiiss.

Amyl Nitrite. Inhalation of this drug produces a rapid though transient rise in intracranial pressure. Wolff²¹ observed dilatation of the cerebral vessels in the cat following inhalation of this drug.

Relief was obtained in 2 women but not in 3 others. It did not relieve a man and once failed to produce a headache in a man.

Calcium. The calcium-potassium balance is said to have an influence on the normal action of the vegetative nervous system. Potassium is an adjuvant to the parasympathetic, and calcium to the sympathetic nervous system. If some cases of migraine are due to the overaction of the sympathetic nervous system, the administration of calcium might be expected to increase the headache. In our series, calcium gluconate (10 cc. of a 10% solution containing 9.3% of the calcium ion) was used intravenously. Two women were benefited twice, 3 others were given doubtful relief; in 3 others no favorable effect was noted; this was also true in 1 man. One woman was helped on 1 occasion and partially relieved

on another; she was repeatedly aided by ergotamin tartrate. In a man and a woman unbenefited by calcium, ergotamin tartrate was successful.

Summary. To the investigator of so paroxysmal a disorder as migraine, the ability to *induce* the headache by artificial measures is an important time-saving factor. In this series no consistent provocative measure was found. Follutein, histamin and large doses of amniotin were sometimes successful.

In the *relief* of the headache, the most striking benefit was obtained by the hypodermic injection of ergotamin tartrate, a drug which is believed to produce vasodilatation by paralyzing the sympathetic innervation. However, such action on the human cerebral circulation has not been proven. Measures supposed to induce vasodilatation of the cerebral vessels did not give invariable relief. Thus mecholin, a parasympathetic (vagus) stimulant did not always prove helpful, though it gave striking relief in a few cases unaffected by ergotamin tartrate. Histamin was observed to produce cerebral vasodilatation in a man during the course of a cerebral operation (Weiss, Robb and Ellis²²), yet it was not of benefit in our series; indeed, this drug was more apt to intensify or provoke the pain. Amyl nitrite, another vasodilator, failed more often than it brought relief. Adrenalin also was often of no benefit. While adrenalin causes dilatation of the pial bloodvessels in animals as a secondary result of the rise in blood pressure, we do not know what effect subcutaneous injection of this drug has on the human cerebral circulation.

The administration of the ovarian follicular hormone, which is known to be lacking in women with migraine, did not give the expected results. The injection of intravenous calcium was also more or less ineffective.

The diversity of results points to the presence of more than one pathophysiologic mechanism in the production of migrainous headache. One is led to believe that vasospasm is probably a secondary effect of, and not a primary factor in migraine.

We wish to express our thanks to the following concerns for their generous contributions of drugs used in this research: Merck and Co., Sandoz Chemical Works, Inc., Sharp and Dohme, Parke, Davis and Co., Eli Lilly and Co., Schering-Corporation, Anglo-French Drug Co. and E. R. Squibb and Sons.

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**NUCLEOPROTEIN AND SPECIFIC TOXIN DERIVED FROM
STREPTOCOCCUS SCARLATINÆ FILTRATE. THEIR
SKIN REACTIONS, CHEMICAL AND IMMUNIZING
PROPERTIES.***

BY MAUD L. MENTEN, M.D., PH.D.,

ASSOCIATE PROFESSOR OF PATHOLOGY,

C. G. KING, PH.D.,

PROFESSOR OF BIOCHEMISTRY,

W. W. BRIANT, JR., M.D.,

DEMONSTRATOR IN MEDICINE AND PEDIATRICS,

AND

LEOLA GRAHAM, M.A.,

RESEARCH ASSISTANT, DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH,
PITTSBURGH, PA.

(From the Department of Pathology and Chemistry, University of Pittsburgh, and
Children's Hospital.)

THIS work was begun for the purpose of studying the pathogenesis of nephritis produced experimentally by toxins of the *Streptococcus scarlatinae*. In order to counteract the comparatively high resistance possessed by experimental animals against the streptococci, various concentrates from the sterile filtrate were injected. Following the injection of certain of the concentrated products, extreme degenerative nephritic lesions were produced in which destruction of tubular epithelium and complete loss of many glomeruli were the outstanding features. Productive glomerular changes were never encountered. The tubular changes were so intense as to suggest the presence in the injected material of toxic substances

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other than that of the specific toxin. The character of these associated toxic substances was revealed when comparable pathologic changes were produced by injection of similarly concentrated products of the uninoculated broth. Protein decomposition products, such as peptones, proteoses, albumoses, etc., occurring in the media and precipitated with the bacterial toxins in the course of the concentration procedures can produce *per se* pathologic changes in the kidney and other parenchymatous organs which simulate lesions due to the toxins alone.

The presence of such non-specific proteins, in our opinion, militates against the assay of toxicity of the bacterial products of the *Streptococcus scarlatinæ* by lethal dosage and handicaps the use of such products experimentally or clinically. We, therefore, deemed desirable the removal of such associated non-specific products as far as possible, from the toxin, before attempting the production of scarlatinal lesions or determination of the lethal dose of the toxin.

Although successful production of scarlatinal renal lesions comparable to those found in the human have been reported with the toxins of the *Streptococcus scarlatinæ* by Duval and his associates,¹ their findings have not been confirmed by Birkhaug and Howard² nor by our experiments.

Technique. Two strains of hemolytic streptococci were used for most of our experiments. One of these (No. 543) was a strain isolated by Dick and Dick and procured from the American Type Culture Company of Chicago in 1929. The second strain was isolated at the Children's Hospital from a postscarlatinal mastoiditis. Six days after exposure to this organism during experimental work, one of us (M. L. M.) developed a typical case of scarlet fever. The toxin from these 2 strains was, as far as could be determined, of equal toxicity. A third strain obtained through the kindness of Dr. Gladys Dick, in 1931, was also employed in later experiments. The medium used was a hormone broth containing 1% peptone and titrated to pH 7.5. In some cases 0.5% gelatin was added, but as this increased the time required for filtration of cultures, its use was discontinued.

To insure optimal aëration, 250 to 300 cc. of broth were placed in 1-liter flasks, inoculated and shaken frequently. Incubation for 5 days gave on fractionation a good yield of specific toxin but very small amounts of the nucleoprotein. Ten to 14 days' growth increased the yield of nucleoprotein, but was not so favorable for specific toxin production. In most experiments the incubated broth, after 5 days' incubation, was allowed to stand overnight. The upper clear supernatant fluid was decanted off and filtered successively through Berkefeld filters V and N. Culturing of such filtrates demonstrated their sterility. The various methods used for the purification and concentration of the toxins have been recently reviewed by Wadsworth and Quigley.³ The outstanding agents employed have been ammonium sulphate, acetic acid, a combination of these two, alcohol in varying concentration and acetone, all of which have been tried by us. In the first series ammonium sulphate in half saturation was added to the filtrate, and the precipitate removed (Precipitate I). To the remaining filtrate additional ammonium sulphate was added to saturation and the resulting precipitate removed (Precipitate II). These 2 precipitates were further purified by reprecipitating twice and by dissolving in a minimal amount of distilled water and reprecipitating with 3 volumes of 95% alcohol. The

addition of 2 volumes of alcohol to the filtrate from Precipitate I resulted in the further formation of a heavy white precipitate, but this had little skin reddening property. Similar treatment of filtrate from Precipitate II resulted in a cloudiness only.

The best results were obtained by precipitation with alcohol in a manner similar to that described by Ando.⁴ Acetone precipitations were consistently darker and greater in quantity. When the medium contained gelatin, the nucleoprotein was first removed by precipitation with acetic acid at pH 4 and centrifugation. The supernatant filtrate was neutralized to approximately pH 7 and varying amounts of 96% alcohol then added with stirring. The resulting precipitates were removed by centrifugation. Two volumes of alcohol sufficed to remove the major part of the toxic material as a skin reaction could not be elicited with the filtrate remaining after the removal of this precipitate. The bulky precipitates obtained with larger amounts of alcohol contained little additional specific protein. The average amount of toxin obtained with 2 volumes of alcohol was 0.3 gm. per liter of filtrate. Variations in amount depended mainly on length of incubation. Minimal amounts were obtained with 48 hr. and optimal with 5 to 6 days' incubation. The crude toxin was concentrated and reduced in volume by taking advantage of the greater solubility in water possessed by it than by the associated contaminants. The crude toxin was extracted with 200 cc. of distilled water per liter of original filtrate. Any undissolved material remaining was removed and dissolved in dilute acetic acid and designated fraction B. The aqueous extract after removal of fraction B was acidified with acetic acid (1 to 3) to pH 4, and the resulting white precipitate, designated as nucleoprotein, removed by centrifuging. The remaining filtrate was neutralized to pH 7 and precipitated with 2 to 1 alcohol. This white precipitate contained the bulk of the specific toxin. Refractionation was repeated 3 times in order to obtain a uniform product. When gelatin-enriched medium was used, the initial addition of acetic acid to pH 4 gave a bulky precipitate which contained not only the nucleoprotein but also many proteins derived from the gelatin. Neutralization of the filtrate resulting after centrifugation and subsequent treatment with alcohol, as outlined above, gave a specific toxin as in the gelatin-free filtrates. The final white precipitate was dried *in vacuo* and averaged 300 mg. per liter. This material gave a positive skin test in susceptible humans when 0.1 cc. of a 1 in 2500 solution or 0.04 mg. was injected intracutaneously. Subsequently the potency was increased to an intracutaneous dosage of 0.1 cc. of 1 to 3400 dilution by more rapid and careful chemical fractionation and drying. By the above chemical manipulation there is a considerable loss of toxin with reduction in solubility. Attempts to concentrate both the original filtrates and the concentrated toxins by means of adsorption with gum arabic, magnesium hydroxid and aluminum hydroxid at various pHs gave evidence of adsorption on the first 2 materials, but the degree of purification was not sufficiently satisfactory to justify further immediate work.

Pregl's micromethods were used in the determination of carbon, nitrogen, hydrogen, ash and phosphorus in the 3 fractions, viz., nucleoprotein, specific toxin and Fraction B. Samples weighing 4 to 6 mg. were used for all analyses.

In addition to the above analyses, optical rotation, reducing sugars, sulphur and moisture were determined on the specific toxin.

For the optical activity 100 mg. of the sample were dissolved in 10 cc. of water and the optical rotation measured in a standard saccharimeter.

Reducing sugars were determined by titration of a known quantity of hydrolyzed solution against Benedict's reagent. Hydrolysis was carried out in 20% hydrochloric acid for 12 hr.

Because of the high phosphorus content of fraction B, it was analyzed for calcium by precipitation of calcium oxalate.

The nucleoprotein fraction was tested for reducing sugar and optical rotation in the same manner as for the specific toxin.

Results of the microanalyses made on the 3 concentrated fractions derived from the filtrate are detailed in Table 1. The nitrogen content (13.53%), solubility characteristics and isoelectric point at approximately pH 4 of the nucleoprotein fraction indicates a typical protein. The low phosphorus and absence of a significant amount of reducing sugar after hydrolysis of the nucleoprotein is probably due to a certain amount of hydrolysis, despite precautions against this. Its group antigenic specificity (discussed later) strongly indicates that it forms an essential part of the streptococcic cell. It gave a positive skin reaction when 0.1 cc. of a 1 to 10,000 concen-

TABLE 1.—ANALYSIS OF 3 FRACTIONS SEPARATED FROM FILTRATE.

	Nucleo- protein, %	Fraction B, %	Specific toxin	
			Preparation 1 %	Preparation 2 %
Nitrogen	11.56	5.19	6.86	5.45
	13.49	5.33	6.91	5.75
	7.58	5.76
Carbon	27.91	8.07	35.86	38.98
	31.71	10.70	36.56	39.20
Hydrogen	3.93	4.10	5.33	6.40
	4.54	4.34	5.77	6.65
	...	4.47		
Ash	6.11	51.01	5.54	3.44
	6.50	51.03	5.92	3.50
	...	51.17		
	...	Chiefly $\text{Ca}_3(\text{PO}_4)_2$		
Phosphorus	0.65	11.52	1.58	
	0.68	11.71	1.64	
		11.72		
Sulphur	0.30	
Reducing sugar . . .	Trace (after hydrolysis)	...	9.50 (after hydrolysis)	
Specific rotation .	$\left[\alpha \right]_{\text{D}}^{20} = -36^\circ$		$\left[\alpha \right]_{\text{D}}^{20} = +20.8^\circ$	

tration was injected intracutaneously in most older individuals. Fraction B, which consisted mainly of acid calcium phosphate associated with both protein and carbohydrate material, was inert on intracutaneous injection. The calcium was largely derived from the medium. The specific toxin corresponds to a glycoprotein, in which the protein is conjugated with a stable sugar group. It is heat-stable and only loses its specific activity after boiling for $1\frac{1}{2}$ hr. No deterioration in the activity of the dried preparation has been found at the end of 3 years. By the method of purification used, the solubility in water and saline of the skin-reddening toxin of the

Streptococcus scarlatinæ was considerably decreased and the potency was much diminished. This observation is in agreement with Ando. Following precipitation by salts, alcohol or acetone, there was a decrease in solubility which was marked if allowed to stand in contact with the precipitating reagents too long. Rapid manipulation was found to be advisable for a high degree of recovery of the readily dispersed protein. Inasmuch as the rate of distribution and physical reactions *in vivo* are conditioned by the degree and ease of dispersion, this factor is considered an important one.

Preliminary standardization of the concentrated toxin on young white pigs, as recommended by Rosenow,⁵ was tried. Considerable variation was noted in different individual animals, some failing to give any response whatever. Suitable animals were roughly $\frac{1}{10}$ as susceptible as the human, and the reaction appeared in 5 to 8 hr. Because of the comparatively low sensitivity of the pig's skin, final standardization had to be made on human subjects. The variation in activity between successive preparations of the toxin was so slight that this preliminary test was not found to be of any advantage. The final standardization was checked against the commercial "Dick" toxin on susceptible and non-susceptible individuals.

Susceptibility tests were made on 319 children up to the ages of 15 at the Children's Hospital, Presbyterian Home and Roselia Home for Foundlings. Intracutaneous injections of 0.1 cc. of commercial Dick toxin, of the concentrated specific toxin diluted 1 to 3400 in saline, and of the nucleoprotein in a dilution of 1 to 10,000 in saline were made. The results with the nucleoprotein are interesting because of the increased percentage of positive reactions obtained with increasing age. Up to 6 months of age, 17.7% positive reactions were found with a rapid increase to 77.8% at the end of the 1st year. After 4 years of age practically all individuals tested gave positive reactions. Varying degrees of redness with edema were observed with the nucleoprotein test.

Positive tests with the specific toxin paralleled those of the Dick test in 95% of the cases. The 5% consisted mainly of positive Dick reactions with negative specific toxin, and can probably be accounted for by the fact that much of the non-specific protein had been removed from the specific toxin. A very small number of cases gave a negative Dick with a positive specific toxin. Slight differences in concentration may account for this discrepancy. The tendency of the Dick reaction to exhibit a slight edema which is generally lacking with the specific toxin we are inclined to attribute to the presence of small amounts of nucleoprotein in the former.

The incidence of susceptibility to scarlet fever at different ages as indicated by our tests with the specific toxin varied considerably in the 3 institutions. This variation depended largely upon the exposure of the inmates to infection. The average percentage of

positive tests for the first year was 8% and no reactions were obtained during the first 6 months of life. There was a rapid rise to 42% during the second year, with a gradually increasing incidence reaching 72% in the 5th year. This was followed by a gradual decline to 27% in the 15th year.

Besides the tests made on the patients at the Children's Hospital, susceptibility reactions of the personnel were also made. The difference in the reactions found in the group of 113 individuals, consisting of resident physicians, nurses and laboratory staff, compared with those of the 60 employees, is interesting. In the former, 47 (41.6%) were negative and 66 (58.4%) were positive. Of the 47 negative reactors, 21 gave a history of scarlet fever. Among the group of 60 employees, only 1 reacted positively, and this individual, a girl aged 20, developed scarlet fever 2 weeks after the test was performed. Only 9 of the 59 originally negative gave a history of scarlet fever.

Attempts to immunize 34 of the 66 positive reactors of the staff group resulted in producing a negative reaction in 20 (58.8%). Of the 34, 16 were immunized with the commercial Dick series of 5 graded doses and after the fifth dose 7 (43.8%) remained positive. The reaction was not altered by a 6th dose. The 2d group of 18 were immunized with 5 doses of specific toxin of increasing intensity comparable to the Dick series. After the 5 doses, 7 (38.9%) remained positive. The reaction was not altered by a 6th dose. Three of these 7, however, became negative after 8 to 10 weekly small doses ($\frac{1}{4}$ to $\frac{1}{10}$ of the 1st immunizing dose). The positive reactors gave reactions with toxin boiled $1\frac{1}{2}$ hr.

The immunizing activity of either preparation (commercial Dick or specific toxin) was about equal, but with neither could 100% of older "positive" individuals be rendered negative.

At St. Paul's Orphanage a group of 50 children between the ages of 6 and 8 were given the 3 susceptibility tests. Of these, 31 reacted positively with both toxins. These 31 reactors were divided into 2 groups for immunization. The 1st group of 20 were given weekly intramuscular injections of 0.5 cc. of the specific toxin, in progressively increasing concentrations. When retested, 3 weeks after the 4th dose, 18 had become negative. The 2d group of 10 received each week 2 similar 0.5-cc. injections at a 1-hr. interval; 8 of these children were negative when tested 3 weeks after the 8th injection. That is, 87% of the 31 positive reactors became negative after 4 weekly injections of the specific toxin. When one compares the results of immunization in these 2 groups, viz., staff of Children's Hospital and younger children at St. Paul's Orphanage, differing widely in age, it is seen that nearly 30% more were rendered immune in the early age group than in the older.

With both the Dick and specific toxin, reactions of varying intensity were observed in practically all of the individuals immu-

ized. The majority of these reactions consisted of local soreness, with redness and more or less edema. Headache and nausea and in 3 individuals scarlatinoid rashes with rise of temperature and constitutional symptoms were also observed. These reactions might occur with different injections, although a few individuals reacted to every dose.

An attempt was made to immunize rabbits against both the specific toxin and nucleoprotein fractions and sheep and goat against the specific toxin. In only 1 of the 3 series of animals injected with nucleoprotein was an antiserum obtained. The 3 surviving animals yielded a potent antiserum which gave a positive precipitin test in dilutions up to 1 to 600. Besides the positive precipitin reaction, agglutination also could be obtained in a titer from 1 to 600 to 1 to 1200 against the 3 strains of *Streptococcus scarlatinae* used, if the experiment was made with freshly drawn serum (15 to 20 hr.) or if guinea pig complement was added. Apparently sufficient complement was present in the fresh serum to suffice for the reaction. Positive agglutination was similarly obtained against all strains of *Streptococcus pyogenes*, including *erysipelatis*. On extending the observations to include streptococcus of various strains of the Holman classification, it was found that positive agglutination was also obtained with *mitis*, *infrequens*, *equi*, *fecalis* and *equinus*. With the following strains, viz., *salivarius*, *anginosus*, *ignavus* and *non-hemolyticus*, no agglutination was obtained. The differentiating feature between the 1st (positive) and 2d (negative) group is the ability of the former to ferment salicin. On this basis the streptococci can be divided into 2 divisions and hemolysis is not a differentiating characteristic. No agglutination was obtained with any of the pneumococci or members of the coli group. It is of interest to note that in the 2 rabbit series in which no antisera was produced, the injections were made during the winter months, as compared to the summer-injected series with positive sera. A more likely explanation for the negative results of immunization is the degradation and chemical change of the nucleoprotein taking place during incubation, especially if the latter be prolonged. Heidelberger and Kendall⁶ have shown that several antigens are present in the acetic acid precipitable protein fraction. The various animals injected with the specific toxin readily developed an antibody, which gave precipitin reaction in fairly high titer with saline suspension of the specific toxin. However, similar precipitation phenomena were obtained when the antisera were used with a suspension of a precipitate obtained from uninoculated broth. It would appear that an immune body had been developed against the associated non-specific proteins derived from the media rather than against the specific toxin. Further proof of this assumption was observed in the complete lack of any neutralizing effect on the

toxin of the antisera. It should be borne in mind that the specific toxin is only a partially purified product. The fairly high solubility of the specific toxin in water (a property made use of in its concentration) also contributes to the difficulty in producing immune bodies.

Two interesting features developed by the work are the results of immunization. The 1st is associated with an antigenic nucleoprotein which gives a positive agglutination in the presence of complement with various strains of streptococcus characterized by the property of fermenting salicin. This nucleoprotein is closely allied to Heidelberger and Kendall's E, F and G fractions extracted from the *Streptococcus scarlatinae* and also with Lancefield's⁷ P nucleoprotein derived from *Streptococcus hemolyticus*. The low phosphorus content, together with high levorotation of our product would identify it more especially with Heidelberger and Kendall's F and G fractions, and implies, as these authors' work indicate, that a degree of hydrolysis had already taken place either during incubation or chemical manipulation (despite precautions against this) or both. Minor differences, such as decreasing percentage of phosphorus, in chemical composition of residues resulting from such degradations must necessarily occur. With a sufficient degree of hydrolysis there will ultimately result an end product devoid of any antigenic property. This we believe to be the explanation of our failure to obtain an agglutinating antiserum with the nucleoprotein in 2 of our 3 series. The strains of pneumococcus which were tested against our antisera were not studied for their fermentation of salicin as the relationship of the agglutinated strains of streptococcus to salicin was only discovered later. The importance of such cellular constituents to metabolism is seen by their relationship to fermentation.

The difference in the results obtained by immunization against the specific toxin in young and older individuals is probably more apparent than real. The fact that many nurses and physicians who persistently show a positive Dick reaction, yet despite continuous contact with scarlet fever, never develop the disease, argues strongly for their immunity. Furthermore, immunization procedures with the Dick series even when repeated fail to develop a negative reaction in these individuals and may even increase the extent of the positive skin reaction. Likewise a certain percentage of cases of scarlet fever are not followed by a negative Dick reaction. One is, therefore, forced to conclude that such individuals, even in the absence of a positive reaction with toxin boiled $1\frac{1}{2}$ hr. (as is occasionally the case), are immune. We have found that altered conditions in the skin, chiefly allergic, may interfere with the Dick reaction to such an extent that the negative skin test is completely masked. Such pseudoreactions (the nature of which are at the

present under investigation and will be reported in a subsequent paper) are undoubtedly responsible for the apparent lack of immunity resulting from immunization procedures in older individuals.

Summary. Chemical and immunizing properties and the skin reactions of the nucleoprotein and specific toxin fractions separated from sterile filtrates of *Streptococcus scarlatinae* have been studied and discussed.

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INCIDENCE OF SKIN DISEASES IN A STUDENT HEALTH SERVICE.

BY ROBERT L. GILMAN, M.D.,

ASSOCIATE IN DERMATOLOGICAL RESEARCH IN THE UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

(From the Student Health Service and the Laboratory of Dermatological Research,
University of Pennsylvania.)

POLLITZER¹ has given us a comparative statistical study of the incidence of skin conditions occurring among private and dispensary patients. More recently, Lane² published his compilation of dermatologic conditions taken from his experience in general practice, and Goodman^{3,4} has undertaken a study embracing almost 1 million diagnoses representing both clinic and private practice. These figures include the findings of previous compilers in some instances, and may be considered as extremely accurate, due both to the large number of cases represented and the time period covered. There is an amazingly close correlation among the results of the different compilers despite the variation in the age and class of patient and the changes from time to time in diagnostic attitudes of the profession.

The present study, utilizing the figures and attendance at our recently organized health service, represents 1126 new diagnoses registered from January, 1932, to January, 1934. A tabular comparison of the results of Lane, Goodman and the present investigation. (Table 1, p. 269.)

The student group study was of an average age of 19, in good general health, and was composed of 90% men students and 10% women

students. The selection of cases covers 2 school years. As might be expected in this type of patient, tinea in some form was by far the most prevalent condition, with acne vulgaris second in occurrence. I believe with the present-day diagnostic conception and the further limitation of the diagnosis "eczema" that tinea is probably first in all tabulations and for this reason its importance is greatly enhanced. The high incidence of acne is a distinct reflection of the age of the group and the threshold of vanity.

TABLE 1.—TEN MOST COMMON SKIN CONDITIONS.

Guy Lane (Private General Practice).	Goodman (Clinic and Private Practice).	Gilman (Student' Health).
1. Dermatitis	1. Eczema	1. Tinea
2. Eczema	2. Tinea	2. Acne vulgaris
3. Impetigo	3. Acne vulgaris	3. Seborrhea
4. Urticaria	4. Scabies	4. Verrucae
5. Acne vulgaris	5. Psoriasis	5. Pyoderma
6. Herpes	6. Seborrhea	6. Dermatitis venenata
7. Verrucae	7. Impetigo	7. Eczema
8. Tinea	8. Urticaria	8. Pityriasis rosea
9. Pruritus	9. Dermatitis venenata	9. Moles
10. Psoriasis	10. Alopecia	10. Herpes zoster

In the diagnosis of tinea (or ringworm) included, of course, are fungus infections of the toes, hands and groin (not necessarily laboratorily confirmed), ringworm of the body, tinea versicolor (of which there were surprisingly few), plantar warts, ringworm of the nails and dyshidrosis. In this group, ringworm of the feet, hands and groin constituted $\frac{2}{3}$ of the cases.

The diagnosis of acne vulgaris was given for the classical picture of this condition, ranging from mildly seborrheic skins with many comedones to the completed ensemble with fully developed pustules. This is probably less than the actual incidence, as I am convinced that fully $\frac{1}{2}$ of the student population has some form of acne vulgaris.

Seborrhea includes in this compilation the usual well-defined seborrhea of the skin and scalp, seborrheic dermatitis and the early seborrheic alopecias of students. This latter condition, apparently on the increase in young men students, accounts for the relatively prominent position of seborrhea in the present tabulation. Verrucae appear high up in the list, due to the students' willingness to avail themselves of the cosmetic aid furnished by the health service.

Pyoderma is a convenient term for almost all simple forms of pyogenic dermatitis which includes "impetigo," mild sycooses, secondary infections and furuncles. Pyoderma (impetigo) occurs in all 3 groups as well as in Tauber's⁵ list of common skin conditions in children.

Dermatitis venenata, by which is meant acute or subacute dermatitis due to some external irritant, *i. e.*, rhus tox., although among the 10 commonest conditions, represents only 4% of the new diagnoses. In this connection I might add that chronic dermatitis

of external origin has been included among the eczemas. Were we to limit ourselves to the true diathetic eczema of adolescents and young adults (Besnier, Rost), the diagnosis of eczema would not appear in our tabulation. However, conforming to the larger concept of eczema maintained by European and some American dermatologists, I have included certain chronic dermatoses of internal and external origin as well as certain cases of circumscribed chronic patchy dermatitis and *neurodermite*.

Pityriasis rosea occurred often enough to include it in the list of 10, and under circumstances highly suggestive of mild contagion. This, too, does not represent the total number of cases, as some were undoubtedly seen in other departments of the service. Moles may be considered in the same light as warts, *i. e.*, the availability of operative relief called forth a high percentage of response. Herpes zoster occurred mainly in a mild and practically painless or asymptomatic form. No association with varicella was noted; in fact, no case of the latter has been seen during the period under study. If one were to exclude both warts and moles from the tabulation, then molluscum contagiosum and herpes simplex would be No. 9 and No. 10 in the list.

It is striking that scabies, pediculosis and psoriasis, although common in Lane's and Goodman's lists, do not appear here. Seven cases of each were seen during the 2-year period. Quite likely the majority of simple parasitic infections were self-diagnosed and self-treated. The scarcity of scabies is striking—and we may expect an "epidemic" at any time. Urticaria was an uncommon symptom-complex in the medical as well as the dermatologic department. The remaining skin conditions usually regarded as of fairly common occurrence were seldom seen due to the limitations of the age of the student group.

The present tabulation is similar to those previously reported and particularly to that of Lane representing a cross-section of general practice. It bears out the contention of Goodman and others that, since 10 skin conditions constitute from 60 to 78% of those seen in practice, they at least deserve that proportionate amount of study and attention by the student and the practitioner.

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GONOCOCCEMIA WITH RECOVERY.

REPORT OF FOUR CASES.

BY CHARLES K. FRIEDBERG, M.D.,

CLINICAL ASSISTANT, MOUNT SINAI HOSPITAL,
NEW YORK CITY.

(From the Medical Department and Division of Laboratories of the Mount Sinai Hospital.)

THERE is abundant evidence that arthritis, tenosynovitis and other commonly observed benign gonorrheal complications result from the invasion of the blood stream by gonococci. Nevertheless, published observations reveal that only rarely are gonococci isolated from the blood in such instances. Recently Filler¹ reported the 7th case of gonococemia recovering without a persisting cardiac lesion. The case of Thayer² and possibly also that of Tapie and Riser³ should be added to these. In addition there have been several instances of gonococemia and endocarditis recovering with a valvular deformity. (Silvestrini,⁴ Dieulafoy,⁵ Marfan and Debré,⁶ Withington,⁷ Perry,⁸ Newman.⁹)

In view of the paucity of such reported cases, it seems of value to report 4 recovered cases of gonococemia (positive blood cultures) occurring in this hospital within the last 2 years. Three of the patients are perfectly well; the fourth, reported in detail by Newman,⁹ developed a cardiac lesion.

Wheeler and Cornell¹⁰ and Garlock¹¹ have each reported a case of gonococemia in which they ascribed recovery to removal of a focus of infection. They believed they had eradicated the original source of the bacteremia by uterine curettage and salpingectomy. In view of these reports it is worthy of note that all of our recoveries occurred under conservative therapy and without any radical method of treating the source of the infection.

Case Reports. CASE 1.—D. K., white (admitted August 1, 1931; discharged September 19, 1931), a 33-year-old waitress, was well until 2 weeks before admission when she developed a sore throat associated with slight cough, nasal congestion and supraorbital pain. Two days later she awoke with severe abdominal pain localized to the left lower quadrant, associated with a temperature of 104° F.

There was nasal congestion and injection of the pharyngeal mucosa. There was moderate tenderness and resistance in the lower abdomen. Pelvic examination revealed a soft, tender, fluctuating mass behind the uterus. The blood pressure was 102/68; hemoglobin, 70%; blood leukocytes, 17,000 (polymorphonuclears, 90%; lymphocytes, 8; monocytes, 2); sedimentation time, 5 minutes. Urethral and cervical smears were negative for gonococci. The blood Wassermann test was negative. Temperature, 103.4° F.; pulse, 120.

A diagnosis of pelvic abscess was made. A posterior colpotomy was performed and 23 ounces of odorless, yellow, creamy pus was obtained which was sterile on culture in routine media. Five days after operation the patient developed joint pains involving the fingers and left elbow. The

joints were moderately swollen, red and extremely tender. The patient had a chill; her temperature rose to 104° F. and her pulse to 146 per minute. A blood culture taken at this time was reported as containing gonococci. On the 13th postoperative day she developed an acute arthritis of the left sternoclavicular joint. There was a faint blowing systolic murmur at the apex of the heart, which later disappeared. The edge of the spleen was palpable. A second blood culture, taken when the temperature was approaching normal, and a blood complement-fixation test were both reported negative. After 3 weeks, patient's temperature was normal, her joint symptoms gradually subsided on treatment with wet dressings, and she was referred back to her physician for physiotherapy. The patient has now been followed for 2 years, and except for chronic pelvic inflammatory disease is well.

CASE 2.—I. S., white (admitted February 20, 1932; discharged March 27, 1932), a 30-year-old housewife, developed swollen red, painful joints, particularly the left knee and right wrist, 1 month before admission. During this period she had intermittent fever up to 102° F., occasional chills, and vomiting. On the day before admission she developed a rash on the arms, legs, hands and feet. The lesions were heralded by a drawing sensation at the site of the lesion, then redness appeared followed by a blackish discoloration and vesicle formation. On the same day she claims to have had about 10 chills.

The temperature was 103° F.; pulse, 114. The patient appeared acutely ill. In the skin of both upper and lower extremities there were numerous pink and purplish papules, singly and in groups. The older lesions appeared bluish-black with superimposed bullæ or pustules. Some of these were dry and covered with crusts. A few lesions were situated on the palmar aspect of the hands and the plantar aspect of the feet. The right wrist, hand and fingers were the site of an inflammatory process. The fingers were abnormally warm, somewhat edematous and tender. The function was almost completely inhibited due to the extreme pain on motion of the affected joints. Over the left elbow there was fullness, warmth and tenderness, and pain on motion. Aside from the presence of a soft, blowing systolic murmur over the apical region of the heart, the remainder of the physical examination revealed no abnormality. The blood pressure was 113/73. The hemoglobin was 63%; erythrocytes, 4,200,000; leukocytes, 16,500 (80% polymorphonuclears, 13 lymphocytes, 4 monocytes, 2 eosinophils). The contents of the bullæ were of serous nature and free from organisms on smear.

The diagnosis was acute general infection (sepsis), infectious arthritis, probably gonorrheal. The skin lesions were interpreted as erythema multiforme, probably of septic origin.

The temperature ranged between 101° to 104° F. for 2 weeks, and then gradually returned to normal. The urine was normal, as was a Roentgen ray of the chest. No focus of infection could be found in the pelvis. The arthritis yielded gradually to treatment by wet dressings and immobilization. Smear of the fluid from the left elbow joint revealed neutrophils containing Gram-negative diplococci. The patient's husband admitted having intercourse with her while he had a subacute gonorrheal urethritis 3 months before hospitalization. A gonococcus was grown from the blood stream but only in the fluid media. The blood Wassermann and gonococcus complement-fixation tests were negative. Roentgen ray of the right wrist showed absorption of the bone at the intercarpal joint. The heart was normal on Roentgen ray and the systolic murmur disappeared. The electrocardiogram showed only an inversion of T in Lead III. With rest in bed, sedatives and the application of a rubber bandage (Bier hyperemia), the joints improved markedly. She was given a course of gonococcus vaccine intramuscularly, following which she was discharged considerably better, afebrile, and showing only some immobility of her joints. Follow-up after a year shows her completely well.

CASE 3.—I. D., white (admitted August 28, 1933; discharged October 8, 1933), a 23-year-old police constable, contracted gonorrheal urethritis 4 months before admission. Two weeks before admission he developed severe pain in the right shoulder and right calf, and generalized aches and pains. The next day he suffered pain in the right forearm and left thumb. Ten days before admission he developed severe pain and slight swelling of the joints of the right foot followed by similar symptoms in the left. At the same time there was a papular eruption with inflammation of the fourth toe of the right foot, and a large area of erythema on the dorsum of that foot. His physician made a diagnosis of gonorrheal arthritis and he was treated by bed rest and hot applications to the affected joints. While the joint pains diminished he suffered marked sweats, fever between 100° to 103° F., and was unable to walk because of pain. On the day of admission he developed swelling of the wrist and a small erythematous area on its dorsal aspect.

The patient appeared acutely ill. His temperature was 104.4° F., his pulse 120 per minute. There were scattered round areas of erythema on the left wrist, left shoulder, right side of neck and chest, thighs and feet. There was a large erythematous area over the dorsum of each foot. Both feet were moderately swollen and hot. There was distinct tenderness over the dorsum of both feet, and pain was referred to this same region on pressure or by moving the toes. A systolic murmur was heard over the apex of the heart; otherwise the examination revealed nothing abnormal. The blood pressure was 126/80. The leukocytes numbered 30,000 (neutrophils 86%, lymphocytes 9, monocytes 5). The sedimentation time was 36 minutes. The urine was normal.

The diagnosis was gonococcemia, gonorrheal arthritis. On the day following admission the cutaneous lesions became more numerous, and in several places assumed a hemorrhagic pustular or vesicular character, making the diagnosis of gonococcemia more probable as similar lesions had been observed in other cases of gonococcal infection. Fluid obtained from one of the skin lesions contained polymorphonuclear leukocytes but no organisms. A tenosynovitis of the right foot developed, but fluid from this region showed no gonococci. The gonococcus complement-fixation test was negative. Blood culture revealed gonococci on all of the fluid media. Fever lasted 2 weeks and then subsided. The joints were treated by wet dressings and gradually improved. The patient also received gonococcus vaccine intramuscularly. After 6 weeks he was able to walk around with only slight pain, which was relieved by arch supports. The sedimentation time was over 2 hours, and patient was discharged to receive physiotherapy.

CASE 4.*—E. S., white (admitted January 15, 1932; discharged February 27, 1932), a 19-year-old, unmarried girl, had a 4 months' pregnancy terminated by vaginal tamponage 3 months before admission. The next day she developed severe abdominal pain in the right lower quadrant associated with fever of 104° F. One week later a curettage was performed, following which she had daily chills with fever rising to 105° F. In addition there were profuse night sweats and progressive anemia requiring a transfusion.

The patient was an undernourished, pale woman, with petechiæ in the right lower conjunctiva and clubbing of fingers. The heart was slightly enlarged to the left, and a short systolic murmur was heard at the apex and a blowing diastolic murmur to the left of the sternum in the fourth interspace. The spleen was felt two fingers below the costal margin. Pelvic examination revealed a slightly patulous eroded cervix with a grumous discharge, thickened adnexæ, and a retroverted and retroflexed uterus. The temperature was 101.8° F. and the pulse 128 per minute. The urine contained albumin, 2 to 5 erythrocytes per high-power field, numerous leukocytes, and occasional hyaline and granular casts. The

* This case was reported in detail by Newman.*

hemoglobin was 62%; erythrocytes, 4,550,000; leukocytes, 5480 (83% neutrophils, 17% lymphocytes). Blood pressure, 108/70. Sedimentation time, 40 min. Cervical smear was negative for gonococci. Blood Wassermann test, negative.

The diagnosis was chronic sepsis (postabortion); pelvic thrombophlebitis.

The patient continued to run a septic course with frequent chills and temperature spiking between 94° and 103° F., and occasionally higher. She was given a transfusion for increasing anemia. Fluoroscopy of the heart suggested aortic insufficiency with a mitral lesion. (There was no history of rheumatism or cardiac ailment preceding the present illness.) A diagnosis of subacute bacterial endocarditis was entertained. Two blood cultures were reported as positive for gonococci. A third and fourth culture were both negative. Gonococcal complement-fixation test was reported 4+ 4 days after admission, 2+ just before discharge. After 3 weeks the temperature returned to normal, spleen receded and urine became normal. Follow-up after 1 year revealed that the patient was symptom-free, married and 5 months pregnant. The blood pressure was 124/68. Cardiac examination showed the presence of a systolic murmur over the apex and a low-pitched diastolic murmur to the left of the sternum.

Diagnosis. The essential features of these cases, as well as of those previously reported, may be gleaned from Table 1. Certain points deserve special comment. As a rule arthritis is present with the onset of gonococcemia. A general gonococcal infection may be present, however, without a simultaneous arthritis. Where, as in our third case and that of Thayer,² no arthritis was present, the diagnosis becomes more difficult. Sometimes the primary infection is already healed and no organisms are found in the genital tract. In such cases the history or recovery of the organism from a metastatic focus (elbow, Case 2) will establish the nature of the primary disease. Blood stream infection is suspected from the general constitutional symptoms, absent in uncomplicated gonococcal urethritis, arthritis or salpingitis. The patients are more acutely ill than a local infection would warrant. Almost invariably patients have chills and high fever, generally of intermittent or remittent character, sweats, anemia, leukocytosis, increased sedimentation rate.

Of special significance are the skin lesions which are almost invariably present. These in themselves are probably not specific for gonococcemia, but in conjunction with other evidences of gonorrheal infection are highly suggestive of a general infection. The lesions occur on the extremities, the trunk and occasionally the neck; the face is spared. They appear as crops of macules or papules, sometimes of hemorrhagic nature. They disappear in 2 or 3 days and may recur. More suggestive are the vesicular or pustular lesions found in Cases 2 and 3 and likewise reported by Jenkins,¹² Cabot,¹³ O'Brien and Bancker,¹⁴ and by Filler.¹ Unlike the cutaneous lesions in other general infections, these contain no organisms. The association of a recent or active gonorrheal urethritis or arthritis with cutaneous lesions in a patient who appears acutely ill should lead to a diagnosis of gonococcemia. On this basis, the diagnosis was made on admission in our most recent case (Case 3) before blood cultures were taken.

TABLE 1.—SUMMARY OF ESSENTIAL CLINICAL FEATURES OF RECOVERED CASES OF GONOCOCCEMIA.

Author.	Age and sex.	General appearance.	Temperature.	Chills.	Arthritis.	Cardiac murmurs.	Cutaneous lesions.			Gonococci in genital tract.	Embolie phlegmona.
							Maculopapular eruption.	Pustules.			
Thayer ²	28♂	99-104	+	..	Systolic	+ abdomen	+	0	
Jenkins ¹²	38♂	Toxic, prostrated	102-104	+	+	...	+ in crops on extremities	+ hand	+	0	
Cabot ¹³	26♀	98-103	+	±	...	0	+ thumb, wrist	+	0	
O'Brien and Bancker ¹⁴ .	21♂	Acutely ill	To 104	+	+	Systolic	0	+ neck, arm, legs	+	0	
Wheeler and Cornell ¹⁰ . .	19♀	Acutely ill	+	Systolic	+ (with purpura) generalized	0	+	0	
Garlock ¹¹	26♀	Acutely ill	To 104	Systolic (apex) Sys.-Dias. (base) (transient)	+ trunk, extremities	0	+	0	
Rubenstein and Israel ¹⁵ .	21♀	102-103	+	+	Systolic	+ trunk, extremities	0	+	0	
Filler ¹	31♀	Acutely ill	+	+	Systolic	+	+ lower extrem.	+	0	
Friedberg (Case 1) . . .	33♀	100-104	+	+	Systolic	0	0	0	0	
Friedberg (Case 2) . . .	30♀	Acutely ill	101-104	+	+	Systolic	+	+	0 (positive from elbow)	0	
Friedberg (Case 3) . . .	23♂	Acutely ill	100-104	+	+	Systolic	+	+	0	0	
Newman ⁹ (Friedberg, Case 4)	19♀	Chronically ill	96-104	+	0	Systolic Diastolic	+	+	

Once this diagnosis or indeed the presence of any general infection is suspected, blood cultures should be made until the diagnosis is confirmed or discarded. Owing to the fact that the gonococcus is a difficult organism to grow, one or two negative blood cultures cannot eliminate the possibility of a gonococcemia. Since chills and high fever are so frequent in this disease, the most opportune time for blood culture is during or just after such an episode. In 2 of our cases the only positive cultures were obtained after chills followed by fever up to 104° F. Cabot¹³ and Rubenstone and Israel¹⁵ specifically mention that their positive cultures were obtained after chills. If no chills are observed, positive results will be obtained most frequently if blood cultures are taken immediately after the temperature has reached a high point, provided this attains approximately 104° F. All of our negative cultures were obtained when these were taken at temperatures below 103° F. It appears that positive blood cultures may be obtained more frequently in cases of gonococcal infection if the presence of a gonococcemia is suspected, if blood cultures are made more opportunely, and if suitable methods for the cultivation of the gonococcus are employed.

The blood culture technique presently employed at the Mount Sinai Hospital laboratories was described by Crohn and Schwartzman,¹⁶ Lichtman and Gross,¹⁷ and by the writer.¹⁸ The important features are the comparatively large quantity of blood withdrawn (21 cc.), the use of both fluid and solid media, and of a variety of media differently enriched in order to favor any organism that may be encountered. The routine procedure in these laboratories is to observe the culture media for at least a week before reporting them as sterile. Rarely do gonococci appear before the fourth day. Where a gonococcemia is suspected, the original fluid cultures are subcultured on ascitic agar even when the smear of the original culture is negative. Since organisms grow on the solid media in the original cultures only when they are present in large numbers, it is probable that in none of our patients were the gonococci abundant in the blood stream as they grew only in the fluid media.

Bacteriologic Technique. The presence of gonococci in the blood culture media was verified in the following manner: When smears revealed Gram-negative diplococci with the characteristic morphology of the Neisserian organisms, subcultures were made onto several media as follows: (1) 1% ascitic-glucose agar (plates and slants); (2) blood agar plates; (3) liver hormone ascitic-fluid 1% agar of pH 6.8 and 7.6 (a local modification of Huntton's beef-heart hormone); (4) plain agar. The media were moist and warm before inoculation of the cultures.

When colonies with a morphology suspicious of gonococci (see below) appeared, generally between 48 and 96 hr., on the liver hormone or ascitic fluid media or both and failed to grow on the plain agar, these colonies were subcultured again on the most favorable media for final identification. Such identification depended upon satisfaction of the final criteria: (1) Failure to grow on plain agar media; (2) poor growth on the blood agar plates; (3) good growth on ascitic-fluid or liver hormone ascitic-fluid agar; (4) characteristic morphology of the gonococci, namely, a delicate growth

of grayish-white, translucent, very finely granular colonies resembling dewdrops which, on smear stained by Gram's method, revealed Gram-negative coffee-bean shaped diplococci; (5) positive agglutination test. The serum for agglutination was a polyvalent gonococcal serum prepared by Lederle. A light suspension of the organisms was employed. Tubes were incubated for 24 hr. at 37° C. Controls of agglutination were run with polyvalent New York Board of Health antimeningococcus serum. A positive result consisted in agglutination of the gonococci up to 1 to 320 with a lower or equal (but not higher) agglutination titer with the antimeningococcus serum.

Wheeler and Cornell¹⁰ have distinguished two types of cases of gonococcemia; those which have consistently positive and those with intermittently positive blood cultures. The former are said to occur in patients with endocarditis and indicate the more serious prognosis. In our experience, blood cultures have been equally intermittent in those cases that recovered and those that resulted fatally because of a gonococcal endocarditis. We believe the time and method of making the blood culture are more significant in determining the bacteriologic findings in gonococcemia than the added presence of endocarditis.

Having established the presence of gonococcal bacteremia, I believe we can predict the outcome with a high degree of accuracy. Thayer¹⁹ and others have shown that those patients with a general infection due to the gonococcus, who succumb, almost invariably have a complicating gonococcal endocarditis. The prognosis therefore depends upon the presence or absence of endocarditis. This can be determined on clinical features alone, without consideration of bacteriologic findings. While, in general, blood cultures may be obtained more consistently in cases with endocarditis, even in these the bacteremia is essentially an intermittent one and, as we have mentioned, positive blood cultures occurred irregularly even in our fatal cases with endocarditis.

According to generally accepted studies, fever, chills, anemia and other constitutional reactions are present in general infections whether a patient has endocarditis or not. The other symptoms, which may be termed specific ones, are definitely referable to endocardial involvement. These specific symptoms consist essentially of embolic phenomena and alterations in heart sounds.²⁰ Under embolic phenomena, we do not include the cutaneous lesions already mentioned, since these lesions are free from organisms and their origin is not necessarily from vegetations on the heart valves. White centered petechiae, when present, are very suggestive of bacterial endocarditis, but they may occur in other conditions. More significant is the occurrence of embolization with infarction of various organs. Embolization is revealed by occlusion of an artery of an extremity, by hematuria and other renal symptoms, hemoptysis and chest pain (due to pulmonary infarction), sudden sharp pain in the left hypochondrium or shoulder (splenic infarction and perisplenitis), and occasionally hemiplegias. Some of these symptoms are, of course, not conclusive of embolization. More direct evidence of endocarditis is found in the sudden development

and alteration of murmurs. A glance at Table 1 will indicate that a transitory systolic murmur is a frequent occurrence in gonococcemia even in recovered cases without endocarditis. For this reason, significance can be attached only to diastolic murmurs, not previously present, which develop in the course of the bacteremia and which remain persistently. Such occurrence in the course of gonococcemia is highly suggestive of the presence of bacterial vegetations on the heart valves. Case 4 in my series developed such a murmur, as well as white centered petechiæ and evidence of nephritis. While this case and a few other similar recoveries with endocarditis have been reported, the diagnosis of gonococcic endocarditis should lead generally to a hopeless prognosis. Conversely the absence of symptoms of endocarditis points almost invariably to a favorable prognosis.

Summary. 1. Four cases of gonococcemia are reported in whom recovery occurred under conservative therapy.

2. Careful clinical observation and the employment of adequate blood culture technique may lead to the more frequent diagnosis of this condition.

3. In the cases thus far reported, recovery generally occurred if there was no complicating gonococcal endocarditis. The latter is recognized by the presence of embolic phenomena and the development of persistent diastolic murmurs.

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Erratum.

In the July issue of the American Journal of the Medical Sciences, on Page 91, Line 4, the sentence should read, "The spleen was examined for kersin by Dr. John G. Reinhold and was found to contain that substance in the proportion of 6.02% of the dried spleen."

BOOK REVIEWS AND NOTICES.

ALLERGY IN GENERAL PRACTICE. By SAMUEL M. FEINBERG, M.D., F.A.C.P., Assistant Professor of Medicine and Attending Physician in Asthma and Hay Fever Clinic, Northwestern University Medical School; Professor of Medicine in the Cook County Graduate School of Medicine; Attending Physician, Cook County Hospital, Chicago. Pp. 339; 23 illustrations and a colored plate. Philadelphia: Lea & Febiger, 1934. Price, \$4.50.

PROBABLY 1 person in every 7 is hypersensitive to some foreign substance and is, therefore, a potential sufferer from one or more of the many clinical manifestations of allergy. The problem of diagnosis and management, therefore, occurs very frequently in the experience of the physician. To afford the practitioner an opportunity to inform himself on the subject, the author set himself the task of preparing a text sufficient for practical purposes, and yet not as exhaustive as the existing complete works for special students in the field. He has on the whole achieved his objective fairly well, in spite of the pardonable tendency of the enthusiast at times to go unnecessarily into detail, and a certain prolixity of style. The practitioner will find the book useful and instructive.

R. K.

PHARMACOLOGY AND THERAPEUTICS. By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S., Late Professor of Materia Medica and Pharmacology in the University of Edinburgh. Tenth edition, thoroughly revised by C. W. EDMUNDS, A.B., M.D., Professor of Materia Medica and Therapeutics in the University of Michigan, Ann Arbor, and J. A. GUNN, M.A., M.D., D.Sc., Professor of Pharmacology in the University of Oxford, Oxford, England. Pp. 786; 75 illustrations. Philadelphia: Lea & Febiger, 1934. Price, \$6.50.

THE classic textbook in its field, this "first severely critical rigorously scientific general text-book to be written in English by an experimental pharmacologist" has maintained its popularity for a third of a century. This, the second edition to be published since Cushny's death, contains a biographical note, "lest an oncoming generation . . . may forget that the Man was greater than the Book." The appearance of the British Pharmacopœia of 1932 has required extensive revisions. The growth of constructive pharmacology is recognized by the inclusion of extensive additions, though many omissions indicate the continuing importance of its destructive and critical function.

E. K.

HYPERTENSION AND NEPHRITIS. By ARTHUR M. FISHBERG, Associate Professor to Beth Israel Hospital; Associate in Medicine, Mount Sinai Hospital, New York City. Pp. 668; 39 illustrations and 1 colored plate. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$6.50.

THIS new volume of a standard work has been extensively revised. The general arrangement of the subject matter is logical and well presented, the style is readable, and the illustrations are well chosen. The book can warmly be recommended as a thoroughly reliable and modern guide to a group of common and important diseases.

B. L.

OBSTETRIC MEDICINE. Edited by FRED L. ADAIR, M.A., M.D., F.A.C.S., Mary Campau Ryerson Professor of Obstetrics and Gynecology, etc., and EDWARD J. STIEGLITZ, M.S., M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Rush Medical College of the University of Chicago, etc. Pp. 743; 24 illustrations and 2 colored plates. Lea & Febiger: Philadelphia, 1934. Price, \$8.00.

THIS volume, edited by an obstetrician and an internist, brings before us the views of a group of 39 distinguished contributors regarding the relation of pregnancy to the commoner diseases which may appear as complications, or in which the pregnancy may be an intercurrent happening. The 12 sections include not only a discussion of medical conditions but also associated diseases of the eye and the skin, and disorders of body mechanics.

The first section considers physiology of pregnancy, physical diagnosis as influenced by . . . pharmacology as limited by pregnancy. Under the title . . . the relationship of heredity and intra-uterine development to subsequent events is brought out, with a discussion of the laws of eugenics and euthenics. The text proceeds through such infectious diseases as tuberculosis and the venereal diseases, and the contagious tropical and parasitic diseases. Following this are excellent discussions of avitaminoses, the lesions of the nervous system, disorders of the respiratory tract, the diagnosis and management of heart disease, and diseases of the arteries.

In the section on disorders of the alimentary tract, well considered discussion of dental lesions and an able section on appendicitis during pregnancy. The chapter on diseases of the kidneys includes a new and logical classification of nephritis in pregnancy with details of the most dependable function tests. Illustrative case histories add much to the discussion of this section. The surgical conditions of the urological tract are fully discussed.

In the important section on disorders of the endocrine balance, the authors stress the thyroid and ovary, constitutional types and diabetes mellitus. The section on disorders of the blood is a very complete recapitulation of the blood dyscrasias in relation to pregnancy; methods of blood study are detailed with explanations of findings. Therapy is fully considered. The final sections deal with the diseases of the skin, orthopedic complications and herniations.

In this unusual book the specialist in either medicine or obstetrics will find much of value in the thorough manner in which the subjects have been handled. Such a coördination of diagnosis and treatment of various pathologic states complicating a normal physiologic process should be of extreme value to the general practitioner who may not have available consultants in many various branches.

P. W.

CHRONIC NASAL SINUSITIS AND ITS RELATION TO GENERAL MEDICINE. By PATRICK WATSON-WILLIAMS, M.D., Hon. Consulting Surgeon in Diseases of the Ear, Nose and Throat, Bristol Royal Infirmary, etc. With a Foreword by SIR HUMPHREY DAVY ROLLESTON, BART., G.C.V.O., K.C.B., Physician Extraordinary to H. M. the King; Emeritus Regius Professor of Physics, Cambridge. Pp. 262; 123 illustrations. Second edition. Baltimore: William Wood & Co., 1933. Price, \$5.00.

ALTHOUGH this volume has as its purpose the elaboration of the author's exploratory-suction technique in the diagnosis of nasal sinusitis, an attempt is also made to trace the processes of focal sepsis and to outline the systemic effects of nasal sinus infections. The account of the pathogenesis of the systemic toxemias and secondary infections due to chronic nasal sinusitis will interest the student of general medicine quite as much as the rhinolo-

gist. Numerous clinical examples, interspersed throughout the monograph, clarify the arguments and will hold the attention of the practical clinician. Reiteration of exploratory-suction technique seems highly desirable in view of the practicability of evaluating the status of every sinus and obtaining adequate cytologic study. The section on endorhinology will offer little to rhinologists in this country, where the procedure has been generally employed for some time, but will offer the beginner an excellent expose of the utility of this instrument. A position of conservatism is maintained in regard to sinus surgery, and the conclusions concerning the efficiency and preferability of pernasal operations seem justified. The use of photomicrographs and plates prepared from anatomical material enhances the text. The volume will prove stimulating reading to the rhinologist mainly because the author has a somewhat fresh view of the commonplaces of rhinology. H. S.

A SYSTEM OF CLINICAL MEDICINE. By THOMAS DIXON SAVILL, M.D. (LOND.). Edited by AGNES SAVILL, M.D., assisted by E. C. WARNER, M.D. Pp. 1063; 162 illustrations. Ninth edition. Baltimore: William Wood & Co., 1933. Price, \$9.00.

THIS book differs from other textbooks of medicine in the manner of its approach to the subject. Instead of a series of descriptions of disease pictures, the presentation is from the standpoint of what the physician finds at the bedside, *e. g.*, acute abdominal pain; its possible causes. That the work has reached its 9th edition is ample proof of its popularity and usefulness. Seventeen authors have contributed to the volume.

R. K.

RED MEDICINE: SOCIALIZED HEALTH IN SOVIET RUSSIA. By SIR ARTHUR NEWSHOLME, K.C.B., M.D., formerly Principal Medical Officer of the Local Government Board of England and Wales, and JOHN ADAMS KINGSBURY, LL.D., Secretary of the Milbank Memorial Fund, formerly Commissioner of Public Charities, City of New York. Pp. 324; illustrated. Garden City, N. Y.: Doubleday, Doran & Co., Inc., 1933. Price, \$2.50.

AN extremely interesting description of what Soviet medical practice aspires to be, and, more especially, what it would like the rest of the world to believe that it now is. For the material here presented is what the authors (neither of whom speaks Russian) were shown, or told, in the course of their Russian tour which lasted a month and was in considerable part spent in travelling 9000 miles. The reader should bear this in mind lest he be misled into unwarranted conclusions by a presentation that is very well and plausibly made. In any event, all readers, medical and lay, will find here much food for thought.

R. K.

ESSENTIALS OF MEDICAL ELECTRICITY. By ELKIN P. CUMBERBATCH, M.A., B.M. (OXON.), D.M.R.E. (CAMB.), M.R.C.P., Medical Officer in Charge, Electrical Department, and Lecturer on Medical Electricity, St. Bartholomew's Hospital, etc. Pp. 508; 132 illustrations and 15 plates. Seventh edition revised and enlarged. London: Henry Kimpton, 1933. Price, 10/6.

THIS edition, clearly describing the fundamental theoretical and practical applications of medical electricity, should be a valuable reference to teachers of physics, especially in courses designed for pre-medical students. The

different electrical circuits are well illustrated by diagrams followed by pictures of different types of electrical apparatus.

The former chapter on high frequency and diathermy has been expanded to 7 chapters. No mention is made of the "inductotherm," a new electrical apparatus for producing artificial fever without electrodes. The practical application of different electrical circuits in various forms of treatment is developed in detail with frequent illustrations. The illustrations of the motor points of the muscles of the body should be useful in the application of electrical currents.

J. W.

THE LYOPHILIC COLLOIDS. (THEIR THEORY AND PRACTICE.) By MARTIN H. FISCHER, Professor of Physiology in the University of Cincinnati, and MARIAN O. HOOKER, Research Associate in Physiology in the University of Cincinnati. Pp. 246; 84 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, \$4.50.

THE writers have for many years been engaged in the study of colloidal phenomena and their application to living matter. They discuss the general nature of lyophilic colloids, chemical application, and biological application. It is the aim of the work to explain "why biologists have not been able to rediscover, in living matter, the laws particularly of the physical chemists; and also why another point of view is due in chemistry if we would understand a host of problems of the existence of which, but not the solution of which, the workers in pure or applied chemistry have long been cognizant." It is only fair to point out that much of the matter discussed is controversial. Some of the authors' views are not generally shared. This is precisely the reason why the interested reader will find it of profit to have the work of Fischer and Hooker so conveniently presented in book form.

B. L.

PHYSICAL CHEMISTRY OF LIVING TISSUES AND LIFE PROCESSES. AS STUDIED BY ARTIFICIAL IMITATION AT THEIR SINGLE PHASES. By R. BEUTNER, M.D., PH.D., Professor of Pharmacology, School of Medicine, University of Louisville. Pp. 337; 79 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, \$5.00.

THE object of this work is expressed in the subtitle. The author has collected the very extensive literature that bears on the artificial imitation of life processes. There are discussed artificial models which reproduce certain phenomena peculiar to living organisms; the physical laws of such models; and the application of these laws to biological problems. The work is divided into several sections: Life as a scientific problem; membranes, osmosis and related forces; life processes related to crystallization or due to surface force; electrical currents in tissues and their relation to life processes; the outlook to future possibilities. It is no sense a textbook, but rather a reference work and one which will stimulate thought and the imagination.

B. L.

BERGEY'S MANUAL OF DETERMINATIVE BACTERIOLOGY. By DAVID H. BERGEY, Formerly of the University of Pennsylvania, Philadelphia. Assisted by a Committee of the Society of American Bacteriologists. With an Index by ROBERT S. BREED, New York Agricultural Experiment Station. Pp. 664. Fourth edition. Baltimore: The Williams & Wilkins Company, 1934. Price, \$6.00.

THE fourth edition in 12 years, this includes the advances made since 1930. Two new genera have been recognized—*Brucella* and *Listerella*, and

Pfeifferella and Actinobacillus have been combined. Fifty new species are included and several omitted, as synonymous with other species. With 100 pages added, this new edition would seem indispensable to bacteriologic laboratories. E. K.

DIET IN SINUS INFECTIONS AND COLDS. By EGON V. ULLMAN, M.D., Formerly Special Lecturer for Biology at the Oregon State College; Instructor at the First Medical Clinic at the University of Vienna, etc. Recipes and Menus by Eliza Mez. Pp. 166. New York: The Macmillan Company, 1933. Price, \$2.00.

DENYING the major rôle of an infectious agent, the author propounds the view that dietetic error is the essential cause of colds. (Yet in the title he speaks of sinus *infections*!) Cure and prevention by salt-low, alkaline, fruit-juice, vegetable-juice, back-to-nature diets are preached with the usual fervor—and paucity of proof—of the diet enthusiast. R. K.

CHINESE MEDICINE. By WILLIAM R. MORSE, M.D., LL.D., F.A.C.S. Vol. XI of *Clio Medica*. Pp. 185; 20 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, \$2.50.

THIS is more than a history of Chinese medicine; it is also a sympathetic and informing account of Chinese philosophy, perhaps the most grotesque and most difficult to comprehend of any of the world's philosophies. Starting in the remote past with a dualistic conception of the universe, China's philosophy has developed in a maze of involved abstract speculation utterly foreign to the Western mind which has its roots in the sane and critical philosophy of the Greeks. The peculiar type of intensive speculation in which the Chinese have indulged for nearly three millenia has undoubtedly retarded the Chinese in a material direction. On the other hand, it has produced a peculiarly high moral dignity that has impressed all foreigners who have come in contact with educated Chinamen. Two different persons, one a medical missionary, one a novelist, told the Reviewer that in the presence of high-bred Chinese they experienced a distinct and uncomfortable sense of racial inferiority, a feeling that no European or American had ever given them.

The book deals interestingly with Chinese anatomy, physiology, diagnosis, based almost exclusively on the pulse, with materia medica, with the practice of medicine and surgery. The drugs used by the Chinese are like those employed in Europe during the Middle Ages; a few, such as Ma Huang (ephedrin), have definite value.

It has been claimed by the Chinese that they discovered the circulation of the blood over 2000 years before Harvey, but the statement probably represents nothing more than a poetic figure of speech. A number of characteristic illustrations and a long bibliography enhance the value of this interesting addition to *Clio Medica*. D. R.

ATLAS OF PATHOLOGICAL ANATOMY, VOL. 1. Compiled by E. K. MARTIN, M.S., F.R.C.S. Pp. 489, mostly illustrations, many colored. Baltimore: William Wood & Co., 1933. Price, \$15.00.

THIS first volume of the Atlas of Pathological Anatomy comprises the drawings of pathological specimens which have appeared as a supplement to the British Journal of Surgery during the years 1926 to 1930.

As the title indicates, the main feature of the book lies in the illustrations, which have been drawn from surgical specimens removed at operation

as well as autopsy material. The specimens have been selected from the Hunterian Museum of the Royal College of Surgeons and several of the better known British university medical museums. This first volume treats of tumors and inflammations of bone, and diseases of the stomach, breast, kidney, gall bladder and bile ducts.

The usual tendency in works of this type is to lay too much stress on the rare and the unusual and it is to the credit of the author that he has included only typical examples of the more common lesions, a fact which, especially for teaching purposes, greatly enhances the value of the book.

There are over 250 plates in the book, of which about half are in color. The majority are of gross specimens, the remainder showing typical microscopic fields. The color plates are unusually well done and give an excellent idea of the tissues as they appeared during life. The specimens illustrated indicate careful selection from a wealth of material. Especially noteworthy are the illustrations of the kidney and the inflammatory lesions of bone. Each plate is accompanied by a concise note on the clinical history, gross appearance and microscopic structure.

There can be no question that this Atlas should be of practical use to the surgeon who so often must base his judgment and form an opinion solely on the gross morbid appearance of the lesion as it confronts him at operation. Certainly also the Atlas would be a valuable addition to the teaching equipment of any medical school. It is planned to continue publication of the Atlas until it includes all of the typical lesions that can profitably be illustrated by drawings of museum specimens.

N. McL.

THE GREEK HERBAL OF DIOSCORIDES. Illustrated by a BYZANTINE A.D. 512; Englished by JOHN GOODYER A.D. 1655; Edited and First Printed A.D. 1933 by ROBERT T. GUNTHER, M.A., Hon. LL.D. Pp. 701; 396 illustrations. Oxford: For author at University Press, 1934. Price, £3, 3s.

STRANGE as it may seem, there has never before been published an English translation of this most famous of all Herbals—in fact no English translation was even made until the Greek text with interlinear English was written out by the famous botanist John Goodyer between 1652 and 1655. It is interesting to speculate what the effect on Gerard, Parkinson and the other English herbalists would have been if this translation had the good fortune of Philemon Holland's Pliny and other classical translations. The present work practically represents Goodyer's translation, the manuscript of which had rested with his botanical library in oblivion in Magdalen College. The interest attaching to this celebrated "Greek work of the first century as understood in Hampshire in the sixteenth" is further satisfied by the reproductions of numerous botanical illustrations done by a Byzantine artist of about 512 A.D. And yet it seems that its chief value rests in now having a Dioscorides available in the vulgar tongue.

E. K.

THE HARVEY LECTURES, 1932-1933. SERIES 28. By various contributors. Edited by DR. EDGAR STILLMAN. Delivered under the auspices of The Harvey Society of New York. Pp. 233; illustrated. Baltimore: The Williams & Wilkins Company, 1934. Price, \$4.00.

THE high level of this well known series is maintained by the following articles: The Constitutional Principle in Clinical Medicine, by Julius Bauer; Similarities Between Diseases of the Vegetable Kingdom and Those of Man and Animals, by L. O. Kunkel; The Nature of the Menstrual Cycle,

by George W. Corner; *Dyspituitarism: Twenty Years Later*, by Harvey Cushing; *The Oxidation of Hemoglobin and Other Respiratory Pigments*, by James B. Conant; *Contributions of Chemistry to the Knowledge of Immune Processes*, by Michael Heidelberger; *Recent Biochemical Studies of Liver Function*, by J. C. Drummone; *Humoral Transmission of Nervous Impulses*, by Otto Loewi.

JAPANESE MEDICINE. By Y. FUJIKAWA, M.D. Translated by JOHN RUHRÄH, M.D. Vol. XII of *Clio Medica*. Pp. 114; 8 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, \$1.50.

If one reads a program of a meeting of the Japanese Society of Internal Medicine and, if at the same time the names of the participants are covered over, one would conclude that the program represented the most distinguished German, English or American medical gathering. And yet it is only about a hundred years, according to Fujikawa's interesting book on Japanese medicine, that Dr. Philipp Franz Siebold introduced German medicine into Nippon. There had been some contact with Dutch physicians in the latter part of the eighteenth century and Ryotaku Mayeno about 1770 began by himself to study the Dutch language, using several Dutch medical works and a dictionary. He mastered the language completely and with several coworkers brought out, under the title *Kaitai Shinsho*, a translation of the *Anatomy of Johan Kulmus*. Subsequently the translators with some others formed the so-called *Rangaku*, which means the Science of Holland (*Ran*, an abbreviation for Holland, and *Gaku*, Science). This school became the basis of the development of European science in Japan. After the Franco-Prussian War a number of German military officers came to Japan and organized medical teaching on the German model. To this day the German influence is paramount and much of the work of the native physicians is published in German, some in English.

The whole development of Japanese medicine from its beginning as an offspring of Chinese medicine to its high state of the present day is discussed concisely in Fujikawa's book, which the excellent translation by Dr. Ruhräh makes very readable. A final chapter, by Amano, deals with the work of such men as Shiga, Takamine, Kitasato, Yamagiwa, Noguchi, Hata and others whose names are known throughout the civilized world.

When one contemplates all that the Japanese have accomplished, especially since Commodore Perry's visit in 1854, one can understand their pride and their utter unwillingness to take second place to any other nation.

D. R.

THE MAMMALIAN RED CELL AND THE PROPERTIES OF HEMOLYTIC SYSTEMS. By ERIC PONDER, Washington Square College, New York University. Pp. 311; 52 illustrations. Berlin: Gebrüder Borntraeger, 1934. Price, Rm. 22.50.

This monograph, of great value for those cultivating the several fields of hematology, has the special advantage of dealing only with those topics in which the author has had extensive experience. Thus while the development of the erythrocyte, its rôle in respiration and the chemistry of hemoglobin are not included, the reader has the satisfaction of knowing that the treatment of such matters as the numbers, size, shape, structure, permeability of the erythrocyte, and its behavior during hemolysis reflects not only comprehension but also largely the results of important original contributions. Even with this self-imposed limitation, however, extensive reference has been required, two or more of the ten chapters apparently being entirely

composed in this way. Any yet incomplete consideration of the literature is the greatest fault to be found with this admirable work. Throughout, the treatment is as mathematical as is possible with a biological subject containing an unknown but considerable number of variables. Though not conducive to "light reading" or to immediate practical results (neither of which goals was sought for), it furnishes for the first time a firm basis for future comparisons and advances. The treatment of the general factors underlying cell lysis and their special application to the erythrocyte will be found especially illuminating. E. K.

THE MEDICOLEGAL NECROPSY. A Symposium held at the Twelfth Annual Convention of the American Society of Clinical Pathologists at Milwaukee, Wisconsin, June 9, 1933. Edited for the Society by THOMAS B. MAGATH, The Mayo Clinic, Rochester. Pp. 167; 63 illustrations. Baltimore: The Williams & Wilkins Company, 1934. Price, \$2.50.

MEDICOLEGAL Pathology in this country suffers from the diversity of laws on the subject in the individual states, and a consequent lack of familiarity with its details on the part of medical men. The 1933 symposium of the American Society of Clinical Pathologists (reprinted here from the American Journal of Clinical Pathology) should go far in remedying several aspects of this defect. Schultz's exposition of our medical-legal system (which might well have been longer) offers strong arguments for the replacement of the archaic, pernicious Coroner's office by the Medical Examiner. The special features of a medicolegal autopsy, its toxicology, and characteristic findings are ably, if at times gruesomely, presented. E. K.

MODERN CLINICAL SYPHILOLOGY. By JOHN H. STOKES, M.D., Duhring Professor of Dermatology and Syphilology in the School of Medicine, University of Pennsylvania, and Professor of Dermatology-Syphilology in the Graduate School, etc., with ten collaborators. Pp. 1400; 973 illustrations. Second edition, revised and entirely reset. Philadelphia: W. B. Saunders Company, 1934. Price, \$12.00.

THE tremendous accumulation of new material in this field has required extensive changes and additions, a revision which the author's connection with the American Syphilis Investigation has peculiarly fitted him to perform. Of the original 23 chapters, 15 have been rewritten and a new chapter on relapse and progression added. Fundamental principles and practical applications of diagnosis and treatment receive equal attention; nor is visceral or neural syphilis neglected. The present book is even more valuable than its first edition. (For Review see Am. J. Med. Sci., 174, 705, 1927.) E. K.

MEDICINE. A VOYAGE OF DISCOVERY. By JOSEF LÖBEL, M.D. Translated from the German by L. MARIE SIEVEKING and IAN F. D. MORROW. Pp. 334. New York: Farrar & Rinehart, Inc., 1934. Price, \$3.00.

A VERY readable, instructive and non-technical approach to the subject of medicine presented in 16 chapters, from the point of view of the historical development of its various branches, such as Anatomy, Pathology, Surgery, Theory of Constitution, Psychoanalysis and so on. Yet the various "ports of call" on the voyage are so well introduced by the opening chapters on medicine and biology and so closely welded together that the unity of medicine becomes apparent, whether to "intelligent layman" reader or the medical student or the busy doctor wishing to get a desirable background

for his life work. By an unfortunate translator's error, the word "typhoid" is regularly rendered "typhus," doubtless due to the German ambiguity on this point. E. K.

EARLY FORERUNNERS OF MAN. A Morphological Study of the Evolutionary Origin of the Primates. By W. E. LE GROS CLARK, D.Sc. (LOND.), F.R.C.S. (ENG.), Professor Elect of Anatomy, University of Oxford; Professor of Anatomy in the University of London, etc. Pp. 296; 89 illustrations. Baltimore: William Wood & Co., 1934. Price, \$5.00.

THIS book seeks to study Man's phylogenetic origin, by visualizing the evolutionary development of the whole group of Primates. By noting and following up the trends manifest in the early generalized Primates, light is thrown on the particular trends of Man's evolution—a more valuable method than comparison with existing primates, which are all terminal products of evolutionary lines. The evidence furnished by the skull, teeth, limbs, brain and so on, methodically presented, should be of especial value to students of comparative anatomy and physical anthropology; to the general reader the chapters on the space and time distribution of the primates and their evolutionary radiations should be of most interest. E. K.

THE ANÆMIAS. By JANET M. VAUGHAN, D.M. OXON., M.R.C.P. (LOND.), Beit Memorial Fellow, The Bernhard Baron Institute of Pathology, The London Hospital, etc. With Notes on Normal and Pathological Erythropoiesis by HUBERT M. TURNBULL, D.M. OXON., F.R.C.P. LOND., Director of The Bernhard Baron Institute of the London Hospital. Pp. 248; 24 illustrations. New York: Oxford University Press, 1934. Price, \$4.00.

THE extensive and productive activity in hematologic studies of the past decade has resulted in a greatly increased output not only of original articles but also of monographic reviews and "present statuses" and here we have just one more. Too short to be a complete statement (and its 350 references are admittedly incomplete and really inadequate), this booklet aims to review the clinical as well as the hematologic aspects of the 49 types of anemia included in the classification. In each type is considered etiology, symptoms, pathologic anatomy, differential diagnosis and treatment. Practical considerations and red cell diameters are stressed throughout, and the most recent literature is included. More important earlier literature is thus sometimes crowded out. Misstatements and generally discarded concepts are few, but one is surprised to find avoirdupois weights mixed with other metric measurements. Clearly expressed, with a more than average accuracy, this volume should be useful for the practitioner who wishes to keep up to date in hematology. E. K.

NEW BOOKS.

International Clinics, Vol. 2, Forty-fourth Series, 1934. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with fourteen collaborators. Pp. 317; illustrated. Philadelphia: J. B. Lippincott Company, 1934. (Price not given.)

A very interesting number, reflecting a truly international list of authors writing on important topics.

Die diätetische Behandlung der Allergie bei inneren Erkrankungen. By DR. CARL FUNCK, Chefarzt der Abteilung für Allergie und Ernährungskrankheiten am Elisabeth-Krankenhaus Köln-Hohenlind. Pp. 92. Leipzig: Johann Ambrosius Barth, 1934. Price, Rm. 2.40.

- The Mammalian Red Cell and the Properties of Hæmolytic Systems.* By ERIC PONDER, Washington Square College, New York University. Pp. 311; 52 illustrations. Berlin: Gebrüder Borntraeger, 1934. Price, Rm. 22.50. (Review, p. 285.)
- The Medical Clinics of North America, Volume 17, No. 6 (Chicago Number—May, 1934). Index Volume.* Pp. 266; 38 illustrations. Philadelphia: W. B. Saunders Company, 1934.
- Letsom. His Life, Times, Friends and Descendants.* By JAMES JOHNSTON ABRAHAM. Pp. 498; illustrated. London: William Heinemann, Ltd., Price, 30/-net.
- Electrokinetic Phenomena and Their Application to Biology and Medicine.* By HAROLD A. ABRAMSON, M.D. Pp. 331; 106 illustrations. New York: The Chemical Catalog Company, Inc., 1934. Price, \$7.50.
- The Anæmias.* By JANET M. VAUGHAN, D.M. (OXON.), M.R.C.P. (LOND.), Beit Memorial Fellow, The Bernhard Baron Institute of Pathology, The London Hospital, etc. With Notes on Normal and Pathologic Erythropoiesis, by HUBERT M. TURNBULL, D.M. (OXON.), F.R.C.P. (LOND.), Director of the Bernhard Baron Institute of The London Hospital. Pp. 248; 24 illustrations. Price, \$4.00. (Review, p. 287.)
- Early Forerunners of Man. A Morphological Study of the Evolutionary Origin of the Primates.* By W. E. LE GROS CLARK, D.Sc. (LOND.), F.R.C.S. (ENG.), Professor Elect of Anatomy, University of Oxford; Professor of Anatomy in the University of London, etc. Pp. 296; 89 illustrations. Price, \$5.00. (Review, p. 287.)
- Die Werke des Hippokrates.* Part 1. Sitten- und Standeslehre für Ärzte (Price, Rm. 2.80); Part 2, Die Altbewährte Kunst / Die Kunst. (Price, Rm. 3.) Pp. 59 each. Stuttgart: Hippokrates-Verlag G. M. B. H., 1934. (To be published in 25 parts costing ca Rm. 100, card binding).
- Le Barbiturisme Aigu et les Antidotismes Gardenal: Strychnine, Coramine, Alcool.* From the Medical Clinic of the Hospital of St.-Sauveur à Lille. By G. CARRIÈRE, Professeur de Clinique Médicale, CLAUDE HURIEZ, Chef de Clinique Médicale, and P. WILLOQUET. Pp. 164; illustrated. Lille: A. Durant, 1934. Price, 30 frs.
- The Management of Fractures, Dislocations, and Sprains.* By JOHN ALBERT KEY, B.S., M.D., Clinical Professor of Orthopedic Surgery, Washington University School of Medicine; Associate Surgeon, Barnes, Children's and Jewish Hospitals, St. Louis, and H. EARLE CONWELL, M.D., F.A.C.S., Orthopedic Surgeon for the Tennessee Coal, Iron and Railroad Company, Birmingham, Alabama, etc. Pp. 1164; 1165 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, \$15.00.
- Spinal Anesthesia. Technic and Clinical Application.* By GEORGE RUDOLPH VEHS, M.D., Salem, Oregon. Pp. 269; 81 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, \$5.50.
- Surgery of a General Practice.* By ARTHUR E. HERTZLER, M.D., Chief, Surgeon, Halstead Hospital; Professor of Surgery, University of Kansas and VICTOR E. CHESKY, M.D., Chief Resident Surgeon, Halstead Hospital. Pp. 602; 472 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, \$10.00.
- Tuberculosis in the Child and the Adult.* By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P., Clinical Professor of Medicine (Department of Chest), University of Southern California, the School of Medicine; Medical Director, The Pottenger Sanatorium and Clinic for Diseases of the Chest, Monrovia, California. Pp. 611; 85 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, \$8.50.

That Heart of Yours. By S. CALVIN SMITH, M.D., Sc.D. Pp. 212; 6 illustrations. Philadelphia: J. B. Lippincott Company, 1934. Price, \$2.00.

Who Shall Survive? A New Approach to the Problems of Human Interrelations. By J. L. MORENO, M.D. Pp. 437; illustrated. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1934. Price, \$4.00.

The International Medical Annual. A Year Book of Treatment and Practitioners Index, 1934. Fifty-second year. H. LETHEBY TIDY, M.A., M.D. (OXON.), F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S., Editors, with 31 contributors. Pp. 579; 101 illustrations, 69 plates, some in color. Baltimore: William Wood & Co., 1934. Price, \$6.00.

This admirable and unique volume again presents to us a review of medical advances of the past year, as seen through wise English eyes. The easy reference allowed by the alphabetical arrangement of topics is supplemented by a good index.

Clinical Miscellany. Vol. 1, 1934. By 10 contributors. Pp. 206; 37 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, \$3.00.

Twenty-two communications from members of the staff of the Mary Imogene Bassett Hospital, Cooperstown, N. Y., presenting reports of a variety and, in part, unusual types of cases, well worked up and commented upon.

The Life of Sir Robert Jones. A Biography of the World's Greatest Orthopedic Surgeon, the Friend of Crippled Soldiers and Children. By FREDERICK WATSON. Pp. 327; illustrated. Baltimore: William Wood & Co., 1934. Price, \$3.75.

NEW EDITIONS.

Medical Dictionary, Part I, English-German. By JOSEPH R. WALLER, M.D., and MORITZ KAATZ, M.D. Pp. 201. Fourth edition. Leipzig: Franz Deuticke, 1934. Price, M. 6.

This pocket-sized book is a complement to Waller's German-English Dictionary. Such a volume should have a useful rôle to fill. Words directly from the Latin have been omitted to save space, yet one finds such strangers as "abactio," "abaptiston," "abbot-surgeon" (Leibarzt), "ablepsy," "abomasum," "aborsement," "absterge," "acarthasia" on the first two pages. Verb. sap!

Modern Clinical Syphilology. By JOHN H. STOKES, M.D., Duhring Professor of Dermatology and Syphilology in the School of Medicine, University of Pennsylvania, and Professor of Dermatology-Syphilology in the Graduate School, etc., with 10 collaborators. Pp. 1400; 973 illustrations. Second edition, revised and entirely reset. Philadelphia: W. B. Saunders Company, 1934. Price, \$12.00. (Review, p. 286.)

The Merck Manual of Therapeutics and Materia Medica. A Source of Ready Reference for the Physician. Pp. 1379. Sixth Edition. Compiled and published by Merck & Co., Inc., 1934. Price, \$2.00.

This well known ready reference *vade-mecum* should require but little recommendation from reviewers. If not allowed to replace larger more comprehensive works, it can be a valuable adjunct; but this potential danger must not be forgotten by the busy practitioner who is the one most apt to use it and to commit this fault.

Pharmacology and Therapeutics. By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S., Late Professor of Materia Medica and Pharmacology in the University of Edinburgh. Tenth Edition, thoroughly revised by C. W. EDMUNDS, A.B., M.D., Professor of Materia Medica and Therapeutics in the University of Michigan, Ann Arbor, and J. A. GUNN, M.A., M.D., D.Sc., Professor of Pharmacology in the University of Oxford, Oxford, England. Pp. 786; 75 illustrations. Philadelphia: Lea & Febiger, 1934. Price, \$6.50. (Review, p. 279.)

PROGRESS OF MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

I. S. RAVDIN, B.S., M.D.,

J. WILLIAM WHITE PROFESSOR OF SURGICAL RESEARCH, UNIVERSITY OF PENNSYLVANIA,
AND

C. G. JOHNSTON, M.S., M.D.,

INSTRUCTOR IN SURGERY, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

HYPERPARATHYROIDISM.

DURING the past 15 years there has been considerable interest in the rôle of the parathyroids in the regulation of the integrity of the structure of bone. As in the case of other glands of internal secretion, the impetus for new and more exact work on the function of the parathyroids followed in the wake of the preparation of active extracts by Collip,¹ Hanson,² Hjort, Robinson and Tendick.³ The results of total ablation of the parathyroid glands and the sequelæ of an increase in the amount of the hormone elaborated by these glands has been studied in man and animals in a number of laboratories and clinics. Despite the volume of work done in this field, the exact action of the parathyroid hormone is still not clear. Many facts have been discovered regarding this intricate mechanism, but the complete picture has not been painted due to a lack of many important details. Data from the experimental laboratory have contributed in a very significant manner to the recent advances made in the diagnosis and treatment of conditions arising from disturbances of parathyroid function.

The advances made in the clinical knowledge of conditions arising from alterations in function of the parathyroid glands have been quite remarkable. Conditions for which there was little hope of alleviation and less thought of an explanation of the cause now have a less pessimistic outlook. The number of articles in the medical literature dealing with the diagnosis and treatment of parathyroid dysfunction has become so great that a comprehensive survey of these in this review is not possible. Several excellent reviews of this subject have already been published (Thomson and Collip,⁴ and Jaffe⁵). It is intended that this review be in the nature of an exposition of certain results of experimental effort and clinical experience germane to the surgical treatment of diseases arising from disorders of parathyroid function. For a more complete discussion of the relationship of the parathyroid glands to calcium and phosphorus metabolism the reader is referred to the review of Thomson and Collip.

The parathyroid glands are small lenticular bodies, measuring from 2 to 8 mm. in length, and lying usually in the neighborhood of the posterior or inferior surface of the thyroid gland. Normally they are firmer than the thyroid gland. In the young they are light pink in color and in older individuals they vary from pink to yellowish gray. While generally found in proximity to the thyroid, there is no relationship to this organ either embryologically or functionally. The thyroid gland arises from the ventral median diverticulum of the pharynx cranial to the second branchial cleft arches, and the parathyroid bodies originate from an entodermal anlage at the 3d and 4th branchial arches. It is thus evident that embryologically they are more closely related to the thymus. Unlike the thyroid, the parathyroids are paired structures, the pair arising from the 3d arch descending more caudad to find their usual position on the dorsolateral aspect of the lower pole of the thyroid gland, the pair arising from the 4th arch descending a much shorter distance to lie close to the superior pole of the thyroid. We have not been able to find any authentic report of their presence within the substance of this structure. The pair from the 3d arch migrate downward with the thymus, in some instances retaining their attachment to the thymus and come to rest attached to or imbedded in the thymus deep in the mediastinum. If the attachment to the thymus is broken early in their development, the glands may be found to lie quite high, sometimes being found as high as the level of the third arch. While the parathyroid glands viewed on an embryologic basis should be paired structures, 2 lying on either side of the midline, actually the number found has been described as from 1 to 12. The variations found may be explained on a basis of fusion, or retrogression of certain of the rudiments, and a splitting in other instances of the rudiments into several components.

The variability in position and number of the parathyroid glands has been well emphasized in a study of human material by Heinbach.⁶ In careful dissections made on 25 human cadavers, Heinbach found from 2 to 6 parathyroids in each case, the position varying widely. The most common position was upon the medial half of the dorsolateral surface of the lateral lobes of the thyroid gland, between the common carotid artery and the inferior constrictor muscle of the pharynx above and the esophagus below, lateral and dorsal to the recurrent laryngeal nerve but not in intimate relationship to it. The parathyroid glands were not, as a rule, adherent to the capsule of the thyroid, but lay most frequently in the areolar tissue outside the true capsule. In addition to careful dissections to study the position and number of the parathyroid glands, Heinbach reviewed the literature on this subject and found similar variations reported by other authors.

The blood supply of the parathyroid glands has been studied by Curtis,⁷ and Curtis and DeQuervain,⁸ who found that these bodies were supplied mainly by the inferior thyroid arteries. However, by injection methods these authors found that even though the inferior thyroid was ligated, the injection mass found its way into the parathyroids in abundance. This work explains why tetany does not result from ligation of the inferior thyroid artery during the course of thyroidectomy, since the parathyroids are amply supplied by a col-

lateral circulation from the vessels of the larynx, pharynx, esophagus, trachea and the cervical fasciæ.

The work of Gley,⁹ in 1892, showed that the extirpation of the parathyroid glands in the dog resulted in tetany. Subsequent work has shown that associated with and preceding the onset of tetany the serum calcium is definitely reduced and the inorganic phosphorus excretion in the urine is decreased. Unless the animal is treated with potent extracts of the gland, with calcium or vitamin D preparations, it soon dies.

The injection in a normal dog in sufficient amounts of an active extract of the parathyroid glands results in a gradual but marked increase in the serum calcium which after a time reaches a peak and then tends to level off or drop slightly. The inorganic phosphorus in the blood after such an injection decreases except when toxic doses of the extract are administered. Then, due most likely to suppression of urinary excretion, the phosphorus of the blood increases. Associated with the changes in the level of calcium and inorganic phosphorus in the blood there is an increased excretion of both these substances through the kidneys. These findings are clear-cut and offer no point of controversy. There is, however, considerable controversy concerning many points, such as the exact location of the source of the calcium and phosphorus excreted, above that ingested. Bauer, Aub and Albright¹⁰ suggest that the bone trabeculæ provide a mobile store of calcium which is decreased by parathyroid hormone administration. A calcium-poor diet in a normal animal also tends to draw on this store of calcium, a calcium-rich diet tending to replace it. Exception has been taken to the statement that it is from the trabeculæ from which calcium is lost after parathyroid hormone administration (Bodansky and Jaffe,¹¹ and Gyorgy¹²), but all authors place the stores of easily mobilized calcium in the bony skeleton.

The serum phosphatase has been shown to be high in osteitis fibrosa cystica, produced experimentally in guinea pigs by parathyroid hormone administration (Bodansky and Jaffe¹³). Similar findings with regard to serum phosphatase have been reported in certain other diseases of the bone, *c. g.*, rickets, generalized osteitis fibrosa cystica and osteitis deformans (Hunter¹⁴). Following injections of parathyroid hormone, the concentration of bone phosphatase is decreased (Page¹⁵).

Many instances of the association of parathyroid adenomata with certain diseases have been reported since Askanazy¹⁶ published a case of osteitis fibrosa cystica with a tumor which was probably of parathyroid origin. Three years after the publication of Askanazy's case, Erdheim reported a case of puerperal osteomalacia with a large parathyroid tumor. Erdheim felt that the tumor was the result of the bone disease, and that it represented compensatory hyperplasia. Hoffheinz¹⁷ reviewed 45 cases of various disorders of bone collected from the literature, together with a case of osteitis fibrosa cystica which he had autopsied, all of which showed enlargement of the parathyroid glands. Of these cases, 17 had definite osteitis fibrosa cystica, while in 8 a diagnosis of osteomalacia was made. Renal calculi were present in a number of instances. Barr and Bulger¹⁸ extended the number of cases of bone pathology with associated parathyroid enlargement by the addition of 29 other cases. Hoffheinz commented on the

association of parathyroid enlargement and bone disease chiefly on the basis of Erdheim's original concept that the changes in the parathyroid were a compensatory mechanism. It may seem unusual that the true mechanism was not earlier recognized and the association of certain bone diseases and the enlarged parathyroids encountered in these did not lead to treatment by parathyroidectomy at an earlier date. This may possibly be explained on the basis that enlarged parathyroids had been reported in patients in whom there was no demonstrable bone pathology. In addition, many cases of bone disease, notably osteomalacia, had been carefully investigated and found to have no parathyroid enlargement, so that any relationship which may seem apparent now could not have been clearly evident twenty years ago. Nevertheless, Schlagenhauser¹⁹ did suggest that the parathyroids be removed in some of the malacic diseases. Since experience has shown that the best results have been obtained in osteitis fibrosa cystica, it is possible that an attempt at extirpation of the parathyroids if done at that time might have served only to cloud the issue, had the parathyroidectomy been performed in a patient suffering from osteomalacia.

The first case reported in which a parathyroid tumor was removed for treatment of bone disease was published by Mandl,²⁰ in 1926. This patient had, previous to the removal of an adenoma of the parathyroid, a parathyroid transplant, which it was thought might relieve the condition, on the basis of Erdheim's theory that the disease was due to parathyroid deficiency. When implantation therapy failed, Mandl explored the neck of the patient and removed a parathyroid adenoma. The following is Mandl's description of his case:

The patient was a street-car conductor, aged 38 years, having a sister who suffered from osteitis fibrosa cystica. He became ill 5 years previously, following a luetic infection. His chief complaint was increasing fatigue in his lower extremities. He became so weak that it became necessary for him to stop work. He had many types of treatment, but except for short remissions the disease progressed. In 1924 he had to resort to the use of crutches. In October, 1924, Roentgen ray showed osteitis fibrosa cystica of the pelvis and femora. He was given thyroid and parathyroid extracts without arresting the progress of his disease. In December, 1924, he suffered a spontaneous fracture of his left femur. In June, 1925, Mandl saw him in his clinic. He was unable to use his lower extremities. Lying down he could not lift his legs or bend his knees. He had pain in his pelvis and legs, and said he could neither stand nor sit, as he felt his pelvis was too weak. He was quite emaciated and, most important, he excreted so much calcium in his urine that it settled out on standing. This excretion of excess amounts of calcium the patient had noted for many months. These symptoms were worse in the colder seasons. On July 2, 1925, 4 parathyroid glands were removed from a dying patient and transplanted into the patient, but he showed not the least improvement. Microscopic examination of the tissue was not done.

Careful search was later made for a palpable tumor but none was found. The patient was willing to submit to a careful search for a parathyroid tumor in the hope that its removal would influence the course of his disease. On July 30, 1925, Mandl removed a yellowish-

brown tumor, almond shaped, sharply demarcated from the surrounding tissue, measuring 25 by 15 by 12 mm., from the area between the left lobe of the thyroid gland and the trachea. It was rather firmly attached to the recurrent laryngeal nerve and was dissected free. It was shelled out from a connective-tissue capsule and had small elevations on its surface.

Examination of the other parathyroid glands revealed the presence of 3 normal appearing glands. The wound healed by primary intention, a temporary recurrent laryngeal nerve paralysis resulting following the operation.

The gland which was removed revealed parathyroid tissue. The alveolar epithelium showed a mosaic pattern with the cells lying one under the other, separated by a fine red line. The protoplasm of the alveolar cells was water-clear and contained nuclei lying free and which contained fine eosinophilic granules. The nuclei were generally bright, round, vesicular and variable in size. Many of the nuclei were 5 times as large as others. The appearance of the alveoli gave a palisading effect, most of the alveoli appearing completely solid. Occasionally a lumen was noted with thin eosin-red contents. Hemorrhage was noted in areas, as well as hematogenous pigment in the connective tissue. Normal parathyroid tissue could not be seen in the section.

The postoperative course showed a marked change in the patient. A few days after the operation it was possible to see with the unaided eye the difference in the excretion of calcium in the urine (9.6 mg. % as compared with 54 mg. % before operation). Four months after operation the bones showed a marked increase in the calcium content; subjectively the patient was much better also. The patient was able to be about with a crutch and a cane, which was impossible for many months before the operation. The pains in the pelvis and legs were gone, and he could move the extremities. He gained weight and looked better, even in a season when ordinarily he would suffer most.

The recognition of the relationship between osteitis fibrosa cystica and parathyroid gland disease in America was made, in 1926, by DuBois.²¹ The patient, a sea captain, aged thirty years, who was seen by DuBois in the Bellevue Hospital in New York, has been extensively discussed. A most complete and painstaking study of his case by Hannon, Shorr, McClellan and DuBois,²² Bauer, Albright and Aub,²³ McClellan and Hannon,²⁴ and Churchill and Cope²⁵ has undoubtedly shed more light on the clinical picture of hyperactivity of the parathyroid glands than any other case.

In 1929, Barr, Bulger and Dixon²⁶ published observations on a case of osteitis fibrosa cystica in which there was an amelioration of symptoms following the extirpation of an enlarged parathyroid gland.

From a review of the literature and observations on the case these authors felt that they were dealing with a definite clinical entity in which (1) rarefaction of bone, (2) multiple cystic tumors in the bone, (3) muscular weakness and hypotonia, (4) abnormal excretion of calcium, (5) formation of calcium stones in the kidneys and (6) a high serum calcium was present. They chose the name of hyperparathyroidism for this symptom complex because of the association of hyperplastic parathyroid tissue and signs suggesting an excess of the hormone

of the parathyroid glands in the body. This term seems to be a very happy one and has been universally accepted. On the basis of later work it became evident that there were many conditions which might fit partially into the chain of symptoms and signs designated by Barr, Bulger and Dixon,²⁶ which were not really the result of parathyroid hyperactivity but which have later come to be classed as hyperparathyroidism by certain writers. Bauer²⁷ has presented a more detailed and complete picture of hyperparathyroidism which narrows the clinical picture to include only the bone disorder known formerly as von Recklinghausen's disease or osteitis fibrosa cystica. We quote Bauer's criterion in full: "Hyperparathyroidism is a disease characterized by definite alterations in the calcium and phosphorus metabolism as well as by certain symptoms and signs. The alterations in the calcium and phosphorus metabolism are:

"1. *An Elevated Serum Calcium.* Serum calcium values as high as 23.6 mg. per 100 cc. have been reported. The normal serum calcium varies between 9.5 and 10.5 mg.

"2. *A Decreased Serum Phosphorus.* Values as low as 1.4 mg. per 100 cc. have been observed, in contrast to normal values of 4 to 5 mg.

"3. *An Increased Calcium Excretion.* The increased excretion of calcium is entirely urinary, the fecal excretion being unaffected.

"4. *An Increased Phosphorus Excretion.* The increased excretion of phosphorus is also entirely urinary. The increased excretions of calcium and phosphorus in 1 reported case were of the same magnitude as those in a normal individual receiving 100 units of an active parathyroid extract per day.

"These alterations in the calcium and phosphorus metabolism may be accompanied by any or all of the following symptoms and signs: (1) polydipsia; (2) polyuria; (3) weakness and loss of strength; (4) constipation; (5) loss of appetite; (6) loss of weight; (7) indefinite muscle and joint aches and pains (commonly diagnosed rheumatism, arthritis or neuritis); (8) bone tenderness; (9) frequent fractures, often following slight trauma; (10) decreased excitability of the nerves; (11) skeletal shortening; (12) kyphosis; (13) bone tumors, frequently diagnosed epulis of the jaw or giant-cell tumor in other bones; (14) kidney or ureteral stones (usually bilateral); (15) characteristic X-ray findings,—such as generalized decalcification, bone tumors, multiple bone cysts, fish-type vertebral bodies, etc.; (16) frequently anæmia with leukopenia."

Unquestionably there are other conditions in which enlarged parathyroid glands have been associated with bony changes, as renal rickets (Langmead and Orr²⁸), osteomalacia (Erdheim²⁹), chronic interstitial nephritis (Harbitz³⁰), multiple myelomata (Barr and Bulger¹⁸), and carcinoma (Klemperer³¹).

Hyperplastic or adenomatous parathyroid glands in these conditions, however, should be considered as a rare finding. In the case of generalized osteitis fibrosa cystica enlargement of the parathyroid glands is the rule. This is exemplified by the case of the sea captain studied by DuBois,²¹ Hannon, Shorr, McClellan and DuBois,²² Bauer, Albright and Aub,²³ McClellan and Hannon,²⁴ and Churchill and Cope,²⁵ in whom repeated searches were made for a period of 6 years before a parathyroid adenoma was found by Churchill.

Ballin³² has attempted to broaden the scope of the term hyperparathyroidism to include Paget's disease and arthritis deformans. This view has been rather strenuously contested by Bauer²⁷ and Jaffe,⁵ chiefly on the basis that in these conditions increased phosphorus and calcium excretion are not found. Whether or not other bone lesions may eventually be found to be associated with true hyperparathyroidism remains to be seen. At the present time the evidence is not convincing.

The renal lesions associated with hyperparathyroidism have been described by Albright, Baird, Cope and Bloomberg.³³ These authors present 3 different types of renal involvement in hyperparathyroidism. They designate their Type 1 as a pyelonephritis, secondary to formation of calcium phosphate stones in the renal pelvis, and suggest that patients with renal stones should be examined for evidences of hyperparathyroidism. Type 2 they designate as those cases having old deposits of calcium in the kidney parenchyma. Type 3 comprise those cases which show signs of acute parathyroid poisoning. The kidney deposits of calcium are found in the parenchyma without chronic renal changes. These cases suffer from anuria and die within a few days.

The case of the sea captain who was the subject of much study did not show evidence of renal calculi when first seen. Calculi did, however, develop during the further course of his disease and showed evidence of Type 2 renal involvement as described by Albright *et al.* The question of whether the calculi which are found in cases of hyperparathyroidism will disappear after parathyroidectomy is intriguing. The possibility of causing solution of these stones by a high phosphorus diet or by the use of sodium acid phosphate, as suggested by Albright, Bauer, Claflin and Cockrell,³⁴ is to be considered, but the possibility of causing further kidney damage with decreasing phosphorus excretion and an increase of phosphorus and calcium in the blood must also be considered. It is interesting that this phase of the subject has not received more widespread attention. It is probable that, should these patients reach a normal phosphorus-calcium metabolism after the extirpation of the offending parathyroid gland and live for several years in good health, there will be reports concerning the status of the kidney stones. In a personal communication, I. Y. Olch reports that a case upon whom he removed a tumor of the parathyroid 4 years ago has shown a definite decrease in the size of her kidney stone.

Hyperparathyroidism as a clinical entity is apparently on a sound basis when the diagnosis is made not only upon the appearance of the bone lesions, but also upon careful metabolic studies. So far the treatment is surgical, since no case has shown improvement on a strictly medical régime. The limits of the clinical entity are clearly defined. Cases of generalized osteitis fibrosa cystica fit into the entity of hyperparathyroidism well. Other bone diseases do not show the striking recovery after parathyroidectomy as do the cases of osteitis fibrosa cystica. Whether other bone diseases will be found to fit the term hyperparathyroidism, it is difficult to say, but in order to introduce any other disease entity into this term, there must be careful metabolic studies made which show that the disease is similar to the conditions found when there is an excess of the hormone of the parathyroid in the organism. The diagnosis of hyperparathyroidism cannot be made save after a careful study of calcium and phosphorus metabolism.

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OPHTHALMOLOGY.

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.,

AND

H. P. WAGENER, M.D.,

ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

THE CEREBRAL CENTERS OF VISION.

INTEREST in the clinical and experimental investigation of cortical localization of the visual functions was revived by the studies of Gordon Holmes and others on visual defects following war injuries to the occipi-

tal lobe. Holmes¹ stated that complete destruction of the striate area on one side caused a complete homonymous hemianopsia through the center of fixation. This finding seemed to contradict the theory of bilateral representation of the macula in the occipital cortex, which theory had been advanced to explain the usual finding in occipital lobe lesions of homonymous hemianopsia with sparing of the macula. Holmes thought that the sparing of the macula usually found in vascular lesions was therefore probably due to overlapping of the arterial supply to the two cuneal areas. He also found that visual hallucinations of the unformed type in the blind field were often associated with lesions of the visual cortex. Holmes was able to demonstrate that defects in the lower field of vision resulted from lesions above the calcarine fissure, that defects in the upper fields were associated with lesions below the calcarine fissure, and that central scotomata, or defects in the macular field, were found in lesions at the occipital pole. A lesion at one occipital pole caused homonymous paracentral scotomata, while injuries to the anterior part of the striate area were followed by peripheral field defects.

These findings lent strong clinical support to the theory of definite and detailed representation of individual portions of the retina in exactly localized areas of the striate cortex. Numerous investigative studies have been undertaken to furnish anatomic and histologic proof of this theory.

Brouwer and Zeeman² studied the nerve fiber and cell degenerations in the primary visual centers following small, experimentally produced lesions of the retina in monkeys. They found that the fibers from the upper half of the retina terminated in the medial part of the external geniculate body, while those from the lower half terminated in the lateral portion. The macular fibers were found to have a very wide distribution in the central part of the geniculate. The peripheral parts of the retina, but not the macula, were found to have small projections in the anterior quadrigeminal body. No visual fibers could be traced into the pulvinar. Brouwer³ had already carried out similar investigations in rabbits and had found an equally definite though somewhat differently located representation of the retinal quadrants in the external geniculate body. Putnam and Putnam, working in Brouwer's laboratory, then excised portions of the striate cortex in rabbits and followed the resultant fiber degenerations back to the external geniculate body. They were able to demonstrate that there was a fixed and definite anatomic projection of the retinal quadrants on the striate cortex and that there was no connection between the striate cortex on one side and the external geniculate of the opposite side.

Following up this work and correlating it with the careful histologic study of two human brains, Putnam concluded that, in man, (1) the optic radiation lies in the inferior longitudinal fasciculus and occupies all of it; (2) the upper quadrant of the retina is projected on the mesial limb of the geniculate body, on the upper portion of the inferior longitudinal fasciculus (optic radiation) and on the upper anterior portion of the striate cortex; (3) the lower quadrant of the retina is represented laterally in the geniculate and inferiorly in the radiation and striate cortex; (4) the macula is represented between the upper and lower fibers in the upper portion of the posterior half of the geniculate and in the posterior part of the striate cortex where its representation is

extensive, and (5) there are apparently no fibers crossing in the corpus callosum from one visual tract to the opposite striate cortex by means of which macular sparing in occipital lobe hemianopsia can be explained.⁵

Putnam was able to show further⁶ that the calcarine fissure does not divide the striate area accurately in two and that it is an unreliable landmark for orientation, more of the visual area usually lying below than above it. He estimated that about 65% of the fibers in the optic nerve arise from the central area of about 2.7 mm. around the fovea, corresponding to about 25° in the visual field, and that about 47% of the optic radiation carries macular fibers, these fibers occupying the center of the radiation. The macular area in the cortex extends about 2 to 3 cm. anterior to the occipital pole.

That the area of the striate cortex reserved for macular vision is relatively very large was shown by Brouwer in a case of homonymous hemianopsia with macular sparing due to a small lesion in the frontal part of the striate area.⁷ Brouwer concludes that the caudal half of the calcarine cortex along with the lateral surface of the occipital lobe serves exclusively for macular projection and that the small frontal area serves for peripheral vision. He believes that the macular area extends farther frontal between the areas for the upper and lower halves of the retina than is commonly believed. Almost the whole of the striate area in man lies on the medial side of the occipital lobe.

Poljak carried on an extensive series of investigations in which he studied the degenerations caused by experimental lesions, both in the external geniculate and optic radiation, and in the striate cortex in monkeys.⁸ He found that the optic radiation was divided into (a) an upper horizontal branch which commences in the mesial segment of the geniculate, carrying fibers from the upper retina and reaching the upper lip of the calcarine fissure by circling above the posterior horn of the lateral ventricle; (b) a lower horizontal branch from the lateral segment of the geniculate and lower half of the retina which goes to the lower lip of the calcarine fissure below the posterior horn of the lateral ventricle, and (c) an intermediate or vertical branch carrying macular fibers to the lateral face of the occipital lobe and to its tip. The most anterior part of the striate cortex was shown to be connected with that portion of the geniculate body which receives fibers from the farthest periphery of the retina. By producing minute lesions in the striate cortex and studying the resultant degenerations, Poljak was able to prove that not only each quadrant of the retina has its separate cortical representation, but each minute portion of the retina is represented in the cortex separately. He demonstrated that complete extirpation of the striate area on one side produced total degeneration of the external geniculate on the same side but had no effect on the external geniculate of the opposite side.

From these data there would seem to be no foundation for the belief in a bilateral cortical representation of the macula. However, it is known that, clinically, homonymous hemianopsia with macular sparing is common in lesions of the occipital lobe. Davison, Goodhart and Needles⁹ report that closure of the calcarine artery will cause partial hemianopsia, inferior quadrantanopsia being present in lesions above the calcarine fissure and superior quadrantanopsia in lesions below the fissure. They state that, according to Foix, complete closure of the

left posterior cerebral artery will result in hemianopsia and alexia. Penfield and Evans¹⁰ find that temporal lobectomy in man will cause complete homonymous hemianopsia without sparing of the macula, due to removal of the optic radiation, while occipital lobectomy results in homonymous hemianopsia with macular sparing. German and Fox¹¹ also found homonymous hemianopsia with macular sparing after occipital lobectomy. In their case all of the area striata was removed except a small portion along the stem of the calcarine fissure. Penfield and Evans, and German and Fox conclude, therefore, that in man there must be a bilateral cortical representation of the macula, or else there must be representation of the macula but no representation of the periphery of the retina anterior to the level of their lobectomy. H. P. W.

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ORIGINAL ARTICLES.

THE SOCIAL INCIDENCE OF RHEUMATIC HEART DISEASE.

A STATISTICAL STUDY IN NEW HAVEN SCHOOL CHILDREN.*

BY JOHN R. PAUL,
ASSOCIATE PROFESSOR OF MEDICINE,

ELIZABETH R. HARRISON,
CLINICAL INSTRUCTOR IN PEDIATRICS,

R. SALINGER,
ASSISTANT CLINICAL PROFESSOR OF PEDIATRICS, YALE UNIVERSITY
SCHOOL OF MEDICINE,

AND

G. K. DEFORD,
NEW HAVEN, CONN.

(From the Departments of Medicine and Pediatrics, Yale University School of Medicine.)

IN a previous paper by one of us¹ the attempt has been made to determine the incidence of rheumatic heart disease in a group of University students, and to relate this incidence to their social and economic background. This study was based on the impression that rheumatic fever is a disease which finds its highest incidence among individuals living under poor hygienic and urban conditions, and that these conditions are usually an expression of poverty. In England, for instance, rheumatic fever has been considered as a disease "of children of the artisan class"² and statements have been

* The expenses of this investigation have been defrayed by a grant from the Milbank Memorial Fund for the study of Rheumatic Fever.

made that: "Although technically the rheumatic infection may not be a 'poverty disease' in that its frequency does not seem to follow absolutely the variations in degree of poverty, yet nothing is more certain than that it is a disease of the poorer classes;"² also that "No disease has a clearer cut 'social incidence' than acute rheumatism, which falls perhaps thirty times as frequently upon the poorer children of the industrial town, as upon the children of the well-to-do."³ Few statistics have been collected upon this point in the United States, probably because sociologic data of this type are more difficult to obtain here than in England, in that distinctions between the different classes are not so clearly defined in this country. The few observations from the United States include those of Faulkner and White,⁴ who obtained data from colleges and private schools, and concluded that rheumatic infections and rheumatic heart disease were relatively less common among this well-to-do group. Swift⁵ states that, "apparently, poverty, malnutrition, and unhygienic surroundings furnish the most favorable soil for the development of this infection. Many cases are seen, however, among well-to-do members of society." Coburn⁶ has also commented on the lower incidence of rheumatic fever in private patients than in the medical wards of the Presbyterian Hospital in New York City.

In our previous study¹ emphasis was laid upon the fact that the most practical present approach to an estimate of the incidence of rheumatic fever was the determination of the incidence of rheumatic heart disease. This method is not ideal because the incidence of rheumatic heart disease may, for instance, be an indication of the type of therapy to which rheumatic patients are subjected, rather than an expression of the actual incidence of the disease responsible for the cardiac lesion. With this limitation in mind, however, the incidence of rheumatic heart disease was determined in a group of 8000 Yale University students. This group represented a higher social and economic plane than that from which most large scale statistics of this type have been derived. In it the incidence of rheumatic heart disease was found to be a little more than half that recorded in similar surveys on industrial workers and military recruits. This furnishes added numerical evidence to support the fact that rheumatic heart disease is less common among well-to-do individuals in the United States than among the rank and file, but the statement from England that no disease has a clearer cut "social incidence" was not strikingly reflected in our figures.

As is obvious, these results may be better interpreted when similar data are available from poverty-stricken districts, and for this reason the present study was undertaken. We have now chosen a younger age group than in the first report, namely, children between the ages of 4 and 18 from public, and private schools of New Haven

and its environs. The attempt has been made to determine the incidence of rheumatic heart disease in this juvenile group from the standpoint of poor urban as opposed to good urban living conditions, and from the standpoint of urban as opposed to rural living conditions.

General Data on the Incidence of Rheumatic Heart Disease Among School Children. In reviewing the literature on this topic from different parts of the world, one is struck by the scarcity of accurate data. There are many school surveys in which "heart defects" and "organic heart lesions" have been recorded, but in only a small number has the attempt been made to determine the actual incidence of cardiac defects of rheumatic origin. However, if we assume that 80% of organic heart disease occurring in children under 16 is rheumatic, it is possible to estimate roughly the incidence of rheumatic heart disease from these statistics. This assumption is based upon figures derived from etiological analyses in relation to age, in large groups of cardiac patients in New York City,⁷ New England,⁸ and Virginia.⁹ Its validity is dependent upon another assumption, that these percentages would exist in parts of the world other than those listed above.

In Table 1 figures obtained from various surveys have been listed. In general, and unless otherwise specified, the age group of the different school populations examined ranges between 6 and 15 years. The observed or estimated incidence of rheumatic heart disease (last column of each of the two sections of Table 1), is found to vary from 1.03 to 20.8 per 1000. These variations, as was emphasized in the previous paper,¹ are probably dependent not only upon the children's age, the geographic location and the social character of the population examined, but particularly upon the diagnostic criteria employed.

In one of the best of the American surveys (Boston, 1926¹⁰) an interesting finding was that in the two most congested urban districts, the percentage of organic heart disease averaged 7 per 1000, while in four less congested districts the average was 4 per 1000. But with the exception of this survey,¹⁰ and another carried out in three counties in the western part of England,^{13,14} we are not aware of other school surveys in which the attempt has been made to relate the incidence of rheumatic carditis to social, economic or racial conditions.

Our first effort was to determine whether or not data obtained from the routine physical examination of school children by school physicians of the City of New Haven would be satisfactory for analysis. It was soon apparent that the actual incidence of rheumatic heart disease could not be determined by this approach, but it was possible to obtain data on certain "cardiac defects" in the poorer group of school children which could be compared with similar data from the better-to-do group.

TABLE 1.—THE OBSERVED AND ESTIMATED INCIDENCE OF RHEUMATIC HEART DISEASE IN DOMESTIC AND FOREIGN SCHOOL CHILDREN.

Surveys in the United States.	School population involved.	Organic heart disease per 1000.	Rheumatic heart disease per 1000.	Foreign surveys.	School population involved.	Organic heart disease per 1000.	Rheumatic heart disease per 1000.
Cincinnati, 1930 (20)	6,960	3.7	2.96*	Gloucestershire, 1927-1930 (13)	53,501	1.03
Boston, 1927 (10)	119,337	5.2	4.5	Bath, 1927-1930 (13)	7,500	1.28
Philadelphia, 1924 (15)	23,671	6.3	5.04*	Wiltshire, 1927-1930 (13)	43,398	1.50
Rochester, Minn., 1931 (16)	1,328† (a)	7.0	5.60*	Somerset, 1927-1930 (13)	42,804	2.17
New York City, 1921 (11)	44,000	8.9	7.12*	Bristol, 1927-1930 (13)	54,673	7.72
Chicago, 1923 (17)	158,826	9.0	7.20*	Transvaal, 1920 (15)	30,000	7.0	5.60*
Philadelphia, 1929 (12)	10,333† (b)	9.1	7.6	Glasgow, 1926 (15)	240,000	7.0	5.60*
Florida, Illinois and Missouri, 1929 (18)	17,974	10.0	8.0*	Hempstead, 1920 (15)	8.2	6.56*
New York City, 1931 (19)	2,691† (c)	11.0	8.8*	Staffordshire, 1920 (15)	70,138	9.6	7.68*
New York City, 1918-1922 (17)	1,336,343	13.9	11.12*	Aberdeenshire (15)	10.0	8.0*
Chicago, 1924 (17)	153,671	15.0	12.0*	England and Wales (15)	366,000	10.0	8.0*
New York City, 1918 (17)	250,000	16.0	12.8*				
Chicago, 1925 (17)	130,260	17.0	13.6*				
				Glasgow, 1926 (15)	10.0	8.0*
				Edinburgh, 1926 (15)	13.0	10.40*
				Birmingham, 1913 (15)	15.0	12.0*
				Germany, 1920 (15)	23.0	18.40*
				Bath, 1926 (15)	23.6	18.88*
				London, 1923 (15)	26.0	20.8*

* Computed on the basis of 80% of "total organic heart disease."

† (a) Ages 11 to 20; † (b) ages 6 to 18; † (c) ages 14 to 17.

*Methods of Examination Employed by School Physicians in the City of New Haven.** The number of children attending public schools in the City of New Haven totals about 34,000 distributed among 65 parochial and public schools. Each year all pupils of the first grade (mostly 5 years of age) and of the fifth grade (mostly 10 years of age) are examined by two school physicians. In recording their data the attempt has not been made by the school physicians to classify heart defects etiologically. As the diagnosis of rheumatic heart disease must rest on certain criteria which do not appear in their records, it has been obviously difficult to estimate its incidence from these figures, but the same method of estimating the rheumatic heart rate from the organic heart rate employed in Table 1, can at least be attempted. Consequently from their data, covering the year 1932, we selected all children with a systolic murmur of the heart thought by school physicians to be "organic" *i. e.*, not a functional murmur. The schools were then divided into two groups. Those attended by children from the more poverty stricken districts of the city were designated as "poorer" schools, and those attended by children from the better districts were designated as "better" schools.

Analysis of the Results of Examinations by School Physicians. Although the diagnostic criteria employed in these examinations by school physicians are limited for our purposes, we believe that the relative incidence of "organic" systolic murmurs (and the fraction of these which may be considered rheumatic) in the two types of schools is of some significance. The latter are shown in Table 2 to be about 1.5 times higher in the "poorer" schools than in the "better" schools.

Results of Our Determinations. In another attempt in which more definite diagnostic criteria were employed, several groups of children were reexamined by one of us (R. S.). The impossibility of covering large groups by this method is offset by the advantage of using our own diagnostic criteria on the entire group.

Our Own Diagnostic Criteria.—While the diagnosis of clear-cut rheumatic heart disease offers little difficulty, the element of clinical judgment is particularly important in border-line cases. Criteria employed for the diagnosis of doubtful cases of rheumatic heart disease were as follows:

1. A history of rheumatic fever, if present, was regarded as of positive importance in the presence of questionable cardiac signs.

2. Some of the signs which have been regarded as of positive significance are given in the order of their importance. The presence of: (a) apical systolic and pre-systolic thrills, or a systolic thrill transmitted to the vessels of the neck. (b) Pre-systolic murmurs, aortic diastolic and other mid-diastolic murmurs. (c) Cardiac enlargement which could not be explained on any other basis. (d) Loud or harsh systolic murmurs best heard at the apex and transmitted laterally.

The diagnosis of congenital heart disease usually rested upon the history, the cardiac findings, the presence of cyanosis, and clubbing of the fingers.

The diagnosis or the interpretation of functional murmurs, of course, offered considerable difficulty. We have followed the view that more definite functional murmurs are generally present at the base of the heart and can be best heard when the patient is prone.

* We are indebted to Mr. Henry J. Schnelle and Miss Margaret Barrett of the Board of Education of the City of New Haven and also to Drs. E. Irene Boardman and Jean Hippolitus for their assistance to us in this work and for the privilege of examining their records.

TABLE 2.—THE INCIDENCE OF SYSTOLIC MURMURS IN CHILDREN FROM "BETTER" AND "POORER" PUBLIC SCHOOLS IN NEW HAVEN.

Type of school.	Grade.*	No. of children examined.	Incidence per thousand.	
			I. Of "organic" systolic murmurs.	II. Of murmurs which may be due to rheumatic heart disease, 80% of I.
"Better"	I	1144	13.2	10.5
	V	1123	14.2	11.3
"Poorer"	I	1863	19.3	15.4
	V	1628	20.8	16.6
Total		5758		

It should be emphasized that under the conditions in which our data were obtained, the application of these diagnostic criteria proved difficult. The majority of the cases of rheumatic heart disease encountered among the populations examined represented mild forms, and unfortunately the diagnosis of just such forms as these requires a large element of personal judgment. It was our effort throughout, however, to include only the more definite cases.

Methods of Examination and Character of Populations Examined. In the groups of children subjected to our own examinations, practically all of the diagnoses were made by two individuals both of whom were familiar with the interpretations which the other placed on various physical signs. Thus 98% of the examinations of the urban school children were performed by one of us (R. S.). All the suburban and rural school children were also examined by one of us (E. R. H.).

Urban Public Schools. Two schools, both of them Junior-High Schools, attended by pupils between the ages of 12 and 14, were selected. One was attended by pupils from one of the poorest districts in the city, the other by pupils from one of the better districts. Only males were examined, and an average of 8 to 10 minutes was spent on each boy. In the "poor" school 332 boys were examined, and in the "good" school 258.

Urban Private Schools. From 4 private schools 168 children were also examined.† The age group covered that of 5 to 18 years. This group is small but represents a large percentage of the entire private school population of New Haven.

Suburban and Rural Public Schools. This group was drawn from the adjacent town of Hamden in which the total school population is about 5000. One of us (E. R. H.) is the school physician for this district. Cardiac examinations were made on boys and girls during the annual routine examinations of the kindergarten (ages 4 to 5), third grade (ages 8 to 10), and eighth grade (ages 12 to 16). About 80% of the children in this group lived in suburban localities, 20% in rural localities.

Analysis of the Results of Our Examinations. Our incidence determinations of rheumatic heart disease are recorded in Figure 1. It is questionable whether they are actually comparable to those of other surveys, because we are not aware of any survey in which such a careful search for the presence of cases of rheumatic heart disease has been made from the original unselected group. It is our belief, therefore, that our incidence determinations would tend

* The majority of the first grade children were aged 5 years, the fifth grade 10 years.

† We are indebted to the following New Haven physicians for the privilege of examining the private school pupils: Drs. E. T. Wakeman, T. S. Evans, and H. B. Arnold.

to be higher than those recorded in Table 1. Nevertheless, it has not been our major effort to compare our incidence determinations with those of other surveys, but rather to compare the incidence found in different sections of our own group.

From Fig. 1 it will be seen that the highest incidence of rheumatic heart disease (48.1 per 1000) was found among male pupils attending a "poor" urban public school, and that this incidence was 1.5 times higher than that found among a similar group of pupils attending one of the "good" urban public schools (31 per 1000). It was 8 times that of the incidence among the best, or private urban schools in this community. It is unfortunate that this last group, representing as it does but 168 private school pupils, is so

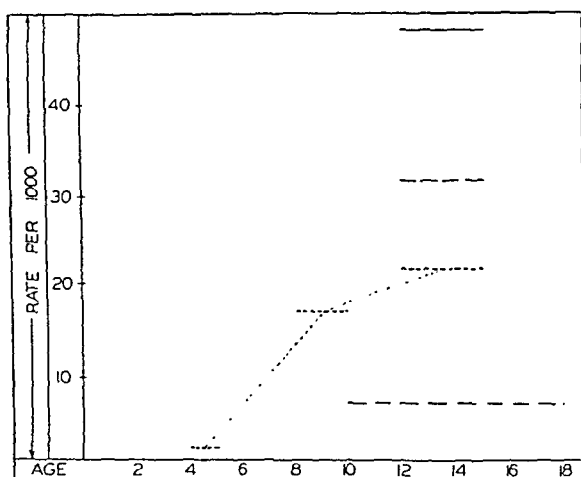


FIG. 1.—The incidence of rheumatic heart disease in public and private urban schools, and public suburban schools.

———— 332 pupils from "poor" urban public school.

----- 258 pupils from "good" urban public school.

..... 2738 pupils from rural and suburban public schools.

Of these 968 = age 12-16; 768 = age 8-10; 1002 = age 4-5.

- 168 pupils from private urban schools.

small and that their ages cover a wider range than that of the public school pupils. As previously mentioned, however, a large percentage of the private school population in New Haven was included in our examinations and, owing to the small size of the group, limitation to a particular age was impractical.

The incidence determinations on public school children from the rural and suburban groups in which no attempt has been made to divide schools into "poorer" and "better" types is also shown in Fig. 1. The rate among suburban and rural public school children of an age comparable to that of the urban group was found to be about 30% lower than that of the "good" urban public school.

Discussion. Our determinations of the incidence of rheumatic heart disease among poverty stricken and other groups of school

children from New Haven and its suburbs seem to bear out the results of our previous studies on University students. They furnish numerical evidence that in and about this particular city of the United States, rheumatic heart disease found its highest prevalence among the poorest children living in an urban environment. As it has been impossible to measure the actual degree of poverty or affluence in the different groups, or the degree to which those who lived outside the city represented a truly rural group, our figures designating actual heart disease rates are only of relative significance. The most striking finding was that rheumatic heart disease was 8 times as prevalent among pupils attending a school from the poorest section of the city as it was among pupils attending private urban schools from the best residential sections.

One gets the impression from these determinations that in New Haven rheumatic heart disease has a low incidence among the small group of children who represent the homes of greatest affluence, but that it has a high general incidence throughout the remaining 95 or 98% of the population. Thus the high incidence found in the "poorer" public school was but 1.5 times that found in the "good" public school. This is a small difference. To some extent this impression partially reflects the English view previously quoted, that rheumatic fever is a disease of "children of the artisan class."²

It is our belief, however, that owing to the nature of the methods employed and the difficulty of applying diagnostic criteria in the border-line cases, our data are still inadequate for broad generalizations on the social incidence of rheumatic heart disease. Our determinations give but a bird's-eye view of the situation. As a further method of increasing knowledge on this subject it has seemed to us that a more intimate study of small communities relating poor and fair living conditions to the prevalence of rheumatic fever is the next step. The report of a study of this latter type will be made in a subsequent paper.

Summary. 1. In an attempt to determine the influence which poverty and urban environments may play as predisposing factors in rheumatic fever, the incidence of rheumatic heart disease has been determined in groups of children between the ages of 5 and 18, attending urban and suburban schools in and about the City of New Haven.

2. Data from the routine examinations of 5758 public school children performed by school physicians suggested that systolic murmurs, presumably of rheumatic origin, were roughly 1.5 times as prevalent among children from the poorer districts than from the better districts of the city.

3. From our own examinations of 758 urban children, the incidence of rheumatic heart disease in a single large public school in one of the poorest districts of the city was found to be 48.1 per 1000. This proved to be 1.5 times as high as that found in a public school in one of the better districts of the city, but 8 times as high as that

found among a smaller group of pupils from urban private schools who came from the best districts in the city.

4. The average incidence of rheumatic heart disease among pupils attending two urban public schools was about twice that recorded among pupils of a similar age group who attended suburban and rural public schools.

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RECURRENCES IN PNEUMOCOCCUS PNEUMONIA.*

BY MAXWELL FINLAND, M.D.,

FRANCIS WELD PEABODY FELLOW IN MEDICINE, HARVARD MEDICAL SCHOOL; ASSISTANT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL, AND VISITING PHYSICIAN, PONDVILLE HOSPITAL,

AND

ALEXANDER W. WINKLER, M.D.,

ASSISTANT RESIDENT IN MEDICINE, NEW HAVEN HOSPITAL; FORMERLY ASSISTANT RESIDENT THORNDIKE MEMORIAL LABORATORY, BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School and from the Medical Service of the New Haven Hospital and the Department of Internal Medicine, Yale University School of Medicine.)

A SURVEY of the literature has failed to reveal any considerable body of data from which one may draw any conclusions regarding the actual immunity against reinfection that is conferred upon an

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individual as a result of an attack of pneumonia. It is of interest, therefore, to review certain features of a series of 57 cases with repeated attacks of pneumonia from which serologically identified pneumococci were obtained during each of 2 or more attacks.

A history of previous attacks has been noted by various writers in from 13.6 to 31% of pneumonia cases.¹ Many repeated attacks have also been encountered rather commonly.^{1,2} As many as 18,^{1b} or even 28 attacks,³ in the same patient have been noted. Among the theories offered to explain this high incidence of recurrences are: (1) That one attack of pneumonia predisposes to another;^{1b,1c,4} (2) that there is a local loss of resistance in a lobe once affected by the disease;^{1b} (3) that there is an individual constitutional predisposition to pneumonia;^{1b,1c} (4) that virulent organisms may persist after recovery and later give rise to reinfection;⁵ and (5) that the individuals attacked have a lower level of natural immunity.⁶ Other explanations have been based on the recent advances in our knowledge of the biologic specificity of different types of pneumococci⁷ and of the immunity resulting from infection or from artificial immunization with these organisms.⁸ Thus, Irons⁶ intimates that the recurrent attacks are each due to a different type of pneumococcus. Cole^{1f} concurs in this opinion but excludes Type III and Group IV cases from this category, the former because of the irregular and low-grade character of the resulting immunity, and the latter because of the heterogenicity of strains within the group.

There are mentioned in the literature only scattered instances of repeated attacks of pneumonia in the same patient with adequate bacteriological data during each attack. Stillman⁹ noted a case of Type II pneumococcus pneumonia in a patient who had just recovered from a Type I pneumonia but was meanwhile exposed to a brother who was suffering from Type II pneumonia. Robertson¹⁰ reported a case of Type I lobar pneumonia, probably resulting from direct laboratory infection, which was followed several months later by Type II lobar pneumonia similarly acquired. On the first day of the second attack this patient showed slight bactericidal power for Type II pneumococci in his blood, presumably indicating that he was not unusually susceptible to these organisms. Cole's case with 18 attacks of pneumonia was typed in the last 7 attacks. Type III was obtained during 4 attacks, and Type I, Group IV and Type II atypical in the others.^{1f} Cole^{1f} and Thomas¹¹ each reported 1 case of recurrent Type I pneumococcus pneumonia in which serum was given during each attack. Cole's case recurred in the same lobe after 8 months; Thomas' case recurred in a different lobe after 1 month. The latter author also noted 2 cases in which pneumonia recurred but was due to a different type. Cecil¹² and Cole^{1f} mention repeated attacks of Type III pneumococcus pneumonia, and the former also speaks of relapses due to the same type occurring after a few days in serum treated cases of Type I pneumonia.

Selection of Cases. The following criteria were used in selecting the cases for this study: (1) Each patient had 2 or more distinct attacks of pneumonia with characteristic physical and roentgenographic findings during each attack. (2) A pneumococcus was isolated and its type identified serologically during each of 2 or more attacks. (3) Each patient was discharged and well before the onset of the succeeding attack, this criterion being used arbitrarily to distinguish "recurrence" from what may be termed "relapse." In several instances, the data relating to additional typical

TABLE 1.—RÉSUMÉ OF CASE HISTORIES OF 20 PATIENTS WITH RECURRENT PNEUMOCOCCIC PNEUMONIA HAVING TYPE I PNEUMOCOCCI IN FIRST ATTACK.

Case number.	Sex.	Age (years).	Consolidation.	Lobes involved.	Termination mode and day.	Interval from previous attack.		Pneumococcus type.	Specific serum, kind and day.	Remarks. (Positive blood cultures, complications, other organisms, etc.).
						Years.	Mos.			
1	M.	18	L	Rl	C 4	..	10	I	S3	Colored.
2	M.	20	B	Rl	C 8	2	10	IV	..	
3	M.	49	L	Rl	L 7	..	3	I	S4	LP = O.
4	M.	52	L	Ll	L 6	3	3	I	..	Mild course.
5	M.	63	L	Rl	L 8	10	9	VII	..	
6	M.	28	L	Lu	C 5	..	7	I	S4	BC I, colored, serum reactions.
7	M.	29	L	Lu	C 5	..	1	I	S3	Sputum = H. Inf., serum reactions.
8	M.	19	L	Rl	L 9	..	1	I	..	BC I.
9	M.	22	L	Rl	C 10	3	1	IV	H3	Onset 1 day postop. (ether, finger amputation).
10	M.	7	L	Rl	E	I	..	BC I, PF I, Empyema, rib resection, syphilis.
11	M.	18	B	Rl	L 16	11	7	XV	..	Rheumatic fever 2 and 1 yr. before; onset with hemoptysis.
12	M.	55	L	Llu	L 13	14	..	I	..	Colored, chronic bronchitis, LP-O; 2 previous attacks.
13	M.	65	B	Rlml	D 15	9	7	III	..	LP-III, PM, chronic nephritis, arteriosclerosis.
14	M.	27	L	Llu	E	18	..	I	..	Empyema, rib resection (chronic and recurred).
15	M.	39	B	RlLl	D 4	11	5	VI	..	Onset 6 days postop. (ether, thoracoplasty) PM, purulent pericarditis (Str. Hem.), healed endocarditis.
16	M.	30	L	Rl	L 8	I	..	
17	M.	41	B	Rm	L 15	11	1	III	..	Onset 2 days after fracture 6th and 7th left rib.
18	M.	37	L	Lu	C 8	12	..	I	S5	BC-I, 2 previous attacks.
19	M.	48	L	Rmu	C 9	10	10	VIII	..	Pseudocrisis 6th day extended 7th day.
20	M.	45	L	Rl	C 8	3	..	I	..	
21	M.	56	L	LluRu	L 10	11	..	II	..	BC-II.
22	M.	42	L	Ll	L 7	I	..	
23	M.	50	L	RlLl	L 5	8	9	I	..	
24	M.	35	L	Lu	C 10	6	..	I	..	Sterile effusion, right.
25	M.	41	L	Ru	C 9	5	10	II	..	
26	M.	20	L	Rl	C 7	8	..	I	S6	BC-II.
27	M.	20	B	RlLl	C 7	..	1 1/2	I	A6	BC-I, 5 previous attacks.
28	M.	14	L	Rl	C 13	..	7	I	..	
29	M.	15	L	Ruml	C 10	..	7	IV	..	
30	M.	19	L	Ruml	C 7	3	10	VII	..	
31	M.	26	L	Ll	C 2	I	A2	8 weeks tachycardia.
32	M.	30	L	Rl	C 8	4	5	II	..	Chronic alcoholism.
33	M.	33	L	Ll	L 13	I	..	
34	M.	36	L	Ru	C 10	2	8	I	..	Chronic alcoholism
35	M.	7	L	Rl	C 6	I	..	Mild course.
36	M.	11	L	Lu	C 6	4	2	II	..	
37	M.	34	L	Rl	L 16	I	S4	BC-I, PF-I, chronic alcoholism.
38	M.	35	L	Rl	D 4	1	2	IV	..	H. Inf. in sputum, DT's, PM HB-O.
39	M.	28	L	RlLl	C 9	I	S5	LP (left and right) = O, H. Inf. and Str. Hem. in sputum, colored.
40	M.	38	L	Ll	D 12	10	..	II	..	Diabetic coma, empyema, PF = Str. Hem.
41	M.	6	L	Rl	C 9	I	..	BC-I.
42	M.	11	L	Rl	C 7	4	8	III	..	

attacks of pneumonia observed in the hospital are also recorded although bacteriological observations were not made. Standard methods were employed in the isolation and typing of pneumococci.^{7a}

Résumé and Analysis of Cases. The more important features of these cases which may be of interest in evaluating local and general immunity are presented in Tables 1, 2 and 3. The features to be considered with respect to each attack are: (1) The character and location of the pulmonary lesion. (2) The duration and mode of termination of the acute disease. (3) The length of the interval between attacks. (4) The bacteriologic findings in the sputum and blood. (5) Specific serum therapy. (6) Complications. (7) Immunologic findings in a few instances where such were made in connection with various other studies.

TABLE 2.—RÉSUMÉ OF CASE HISTORIES OF 18 PATIENTS WITH RECURRENT PNEUMOCOCCIC PNEUMONIA WITH TYPE II OR III IN FIRST ATTACK.

Case number.	Sex.	Age (years).	Consolidation.	Lobes involved.	Termination mode and day.	Interval from previous attack.		Pneumococcus type.	Specific serum, kind and day	Remarks. (Positive blood cultures, complications, other organisms, etc.)
						Years.	Months.			
21	M.	25	L	Rlm	C 8	II	S4	LP = O, serum sickness.
		25	L	Rlm	L 8	..	6	I	..	LP = O.
22	F.	13	L	Rm	C 6	II	..	
		17	L	RILl	C 6	4	6	I	..	
23	F.	20	B	RuLu	C 5	4	0	II	..	Miscarriage (7 mos.) 2 weeks after crisis.
		22	L	Lu	C 8	1	9	I	S6	Pseudocrisis 6th day, 8 mos. pregnant.
24	M.	43	B	L Lu	C14	II	..	
		55	L	RlmLlu	D 4	11	4	Pn.	..	Onset after 1 month congestive cardiac failure; PM:HB-O.
25	M.	44	L	Ru	C 8	II	..	
		45	L	RI	L 5	..	5	IV	..	
26	M.	14	L	LI	C 7	II	..	
		16	L	Lul	C 7	1	11	I	..	
27	M.	13	L	LI	L 7	II	..	
		13	B	LI	L ?	..	2	IV	..	Lung abscess, cleared gradually.
28	M.	39	L	RmLI	L13	II	A4	BC = II; Pn IV (no Pn II) in sputum after 6th day.
		40	L	Llu	L14	..	9	II	..	
29	F.	48	L	Lul	L 5	II	A2	BC = II, colored.
		48	L	RI	D 5	..	3	I	..	BC = I.
30	M.	18	L	Ru	C 4	?	..	II	A4	4 previous attacks.
		19	L	Ru	C 7	1	..	V	..	
31	M.	43	L	RI	L 5	II	A3	Sterile pleural effusion, right. Serum sickness.
		44	B	RILl	C 8	..	7	II	..	
32	M.	36	L	Ru	C10	II	..	Acute and chronic alcoholism.
		38	L	RI	D24	2	1	III	..	Pericarditis.
33	M.	29	L	LI	C13	III	..	Otitis media.
		41	L	RI	C10	11	8	I	S2	
34	M.	44	B	RI	C 5	III	..	1 day postappendectomy (ether).
		48	B	RILl	D 4	3	9	I	..	1 day postthyroidectomy (local) for angina pectoris.
35	M.	12	L	RI	L 7	III	..	Onset 6th week after pertussis, colored.
		13	L	Lu	L 4	..	24	II	A3	
36	M.	58	L	RI	C 6	III	..	Urine precipitin Pn III.
		62	L	LI	L 6	4	2	I	S2	Urine precipitin Pn I, serum sickness.
37	M.	66	L	RILl	C 9	30	..	III	..	Left sterile pleural effusion, chronic alcoholism and arteriosclerosis.
		69	B	RILl	C 2	3	2	III	..	
38	M.	59	L	Ruml	E	III	..	Empyema PF = III.
		62	L	Ru	D26	2	10	IIa	..	Heart block and congestive failure.

TABLE 3.—RÉSUMÉ OF CASE HISTORIES OF 19 PATIENTS WITH RECURRENT PNEUMOCOCCIC PNEUMONIA WITH PNEUMOCOCCUS OTHER THAN TYPE I, II OR III IN FIRST ATTACK.

Case number.	Sex.	Age (years).	Consolidation.	Lobes involved.	Termination mode and day.	Interval from previous attack.		Pneumococcus type.	Specific serum, kind and day.	Remarks. (Positive blood cultures, complications, other organisms, etc.).
						Years.	Mos.			
39	M.	32	L	Rl	L11	IV	..	Pseudocrisis 6th day.
		35	L	RlmuLl	L 9	3	0	I	..	
40	M.	9	L	Ll	C 6	3	0	IV	..	Left sterile pleural effusion.
		9	L	Ll	C 6	..	5	Ila	..	LP = O.
41	M.	38	L	Rlmu	E	IV	..	H. Inf. in sputum, bronchopn. Ll (Str. Hem.) 2 months later.
		47	L	Lu	D 7	0	2	I	..	BC = I, PM jaundice.
42	M.	14	L	Ll	C10	IV	..	LP = O, H. Inf. in sputum.
		15	L	Ll	L11	1	..	IV	..	H. Inf., Str. Hem. and B. muc. caps. in sputum.
		16	L	Rm	C 8	1	..	IV	..	
43	F.	22	L	Ll	L 6	15	..	IV	..	Chronic bronchitis.
		24	L	Ll	L 6	1	8	IV	..	Tonsillitis.
44	M.	12	L	Ll	C 6	3	..	IV	..	Chronic bronchitis, pseudocrisis 4th day.
		13	L	Rl	C 4	..	10	No satisfactory bacteriology.
		13	L	Ll	C 6	..	1½	
45	M.	2	L	LlRl	C 6	1	..	IV	..	Chest clear 2d week.
		2	L	LlRl	L 5	..	1	IV	..	Chest clear 3d week, otitis media.
		2	L	Ll	C 5	..	1	IV	..	Chest clear 2d week.
		2	L	Ll	C 3	..	1	No satisfactory bacteriology.
46	F.	22	L	Lu	L 6	IV	..	
		32	L	Rl	L 7	10	6	VIII	..	
47	M.	21	L	RuLl	L12	IV	..	Colored, syphilis, jaundice.
		31	L	Rl	C 3	9	2	VIII	..	BC = VIII.
48	F.	56	L	Lu	L 9	1	..	IV	..	Hypertension, 2 previous attacks.
		63	L	Lul	D18	7	..	III	..	Delirium, fell from bed and fractured femur 11th day.
49	M.	28	L	Ru	C 9	Acute and chronic alcoholism.
		30	L	Ru	C 7	2	2	IV	H3	
		36	L	Rul	L 7	6	..	I	A4	
50	F.	29	L	Rl	C 9	1	..	IV	..	Many previous attacks, asthma; chronic bronchitis.
		37	B	Rl	C 7	7	4	II	..	
51	M.	31	L	Rl	L 8	IV	..	Asthma and chronic bronchitis.
		39	L	Ll	L10	7	9	I	..	Chronic alcoholism.
52	F.	36	B	Rl	L10	IV	..	Decompensated rheumatic heart.
		38	B	Rl	L 6	2	..	X	..	Cardiac decompensation.
53	M.	14	L	Ll	C 7	2	..	VII	..	3 previous attacks.
		16	L	Rm	C 7	2	..	Pn	..	
54	M.	40	L	Rl	C15	VIII	..	Colored, right sterile effusion.
		40	L	Rul	E	..	3	I	A7	Empyema, PF I.
55	M.	12	L	Rl	C 5	VII	A4	
		13	L	Rl	C 4	..	11	I	A3	
56	F.	22	B	Rl	L 6	IV	..	
		24	L	Rl	C 5	2	..	I	K4	
57	M.	50	B	RlLl	C 8	Ila	..	Str. Hem. in sputum.
		50	B	RlLl	L16	..	6	IV	..	Str. Hem. in sputum.

EXPLANATORY NOTE. Tables 1, 2 and 3.

Cases 17, 18, 20, 31, 35, 36, 37, 55 and 57 are from the New Haven Hospital.

Cases 3, 20 and 39 were previously reported by Thomas.¹¹

Case 13 was reported by Kohn, L. A. (J. A. M. A., 85, 1888, 1925) from the Peter Bent Brigham Hospital.

Abbreviations Used Under Various Headings.

Sex: M = male; F = female. Consolidation: L = lobar; B = patchy (bronchopneumonia). Lobes: R = right; L = left; l = lower; u = upper; m = middle. Termination: C = crisis; D = lysis; D = died; E = empyema; "day" = days after onset. Type: IV = No agglutination with Type I, II or III; Pn = No agglutination with Types I-XX (incl.). Serum: Kind: S = Unconcentrated, homologous type antiserum; H = Huntoon's antibody (Types I, II and III); A = Felton's concentrated antibodies (Types I and II); K = Keyes' chicken serum. Remarks: BC = Blood culture (sterile cultures are not noted); O = Sterile; I, II, etc. = Pneumococcus Type I, II, etc.; LP = culture of lung puncture material; PF = Pleural fluid; PM = Postmortem; HB = Heart's blood culture; H. Inf. = Hemophilus influenzae; Str. Hem. = Streptococcus hemolyticus; B. muc. cap. = Bacillus mucosus capsulatus (Friedländer).

Age, Sex, Color. Most of the patients were adult white males. There were 5 patients under 12 and 7 patients over 50 years of age during the first attack. Nine of the patients in this series were females; 7 of the males and 1 of the females were colored.

Character of the Pulmonary Lesions. (Table 4.) The pulmonary lesion in 72% of the cases was lobar in distribution during each observed attack. There were 3 such attacks in each of 6 patients and 4 in 1 case. In all but 4 of the remaining cases an "atypical" or patchy lesion (bronchopneumonia) was observed only during the recurrence. The 7 cases having the same pneumococcus type (excluding Group IV) in both attacks all had lobar pneumonia in the first attack. The lesion during the recurrence in these cases was lobar in 4 instances and patchy in the others.

TABLE 4.—COMPARISON OF EARLY ATTACKS AND RECURRENCES.

ALL CASES.		
<i>Pulmonary Lesion:</i>		
In first attack.	In recurrence.	Number of cases.
Lobar	Lobar	41 (72%)
Lobar	Atypical	12
Atypical	Lobar	2
Atypical	Atypical	2

NON-FATAL CASES.

<i>Duration of Acute Disease:</i>	Number of cases.
Same (\pm 1 day) in both attacks	23 (45%)
Recurrence 2 or more days longer	11
Recurrence 2 or more days shorter	17

Mode of Termination:

First attack by.	Recurrence by	
Crisis	Crisis	25
Lysis	Lysis	12
Crisis	Lysis	8
Lysis	Crisis	7
Crisis	Empyema	1
Empyema	Lysis	1

FATAL CASES.

Case No.	First attack.		Fatal attacks.
	Mode of termination.	Complications.	
19	Crisis	Str. Hem. in sputum	Diabetic coma; Str. hem. empyema.
23	Crisis	Prolonged congestive heart failure.
31	Crisis	Acute alcoholism	Pericarditis.
33	Crisis	Postoperative	Postop.; Str. hem. pericarditis and mediastinitis.
6	Lysis	Chronic nephritis, arteriosclerotic heart.
18	Lysis	Bacteremia, alcoholism	Delirium tremens.
28	Lysis	Marked bacteremia	Bacteremia.
47	Lysis	Fracture femur.
7	...	Empyema	Postop.; pericarditis; endocarditis.
37	...	Empyema	Heart block, cardiac failure.
40	...	Empyema	Jaundice, bacteremia.

Secondary Pneumonias. In 16 instances the attacks of pneumonia were secondary to conditions other than common colds. These attacks were secondary to operative procedures in 4 instances, congestive heart failure in 5, asthmatic attacks in 4 instances and fractured ribs, pertussis and diabetic coma each in 1 instance. The pulmonary lesion in 9 of these secondary attacks was patchy in character. In addition, 7 of the patients were chronic alcoholics who were more or less under the influence of alcohol at the time of each admission.

TABLE 5.—COMPARISON OF LUNG INVOLVEMENT DURING THE FIRST AND SUBSEQUENT OBSERVED ATTACKS OF PNEUMONIA.*

	Lung involved during first attack.	Lung involved during recurrence.									Total (first attack).
		Right lung.				Left lung.				Bilateral.	
		Lower.	Upper and / or middle.	Entire.	Total.	Lower.	Upper.	Entire.	Total.		
Right Lung	Lower	6	1	2	9	5	2	0	7	6†	22
	Upper and / or middle	2	2	1	5	0	0	0	0	1	6
	Entire	0	1	2	3	0	1	0	1	0	4
	Total	8	4	5	17	5	3	0	8	7	32
Left Lung	Lower	6	2†	0	8	3	1	1	5	2†	15
	Upper	1	4†	0	5	0	1	1	2	0	6
	Entire	1	0	0	1	0	0	0	0	3	4
	Total	8	6	0	14	3	2	2	7	5	26
	Bilateral	1	0	0	1	2	1	1†	4	2†	7
	Total (recurrence)	17	10	5	32	10	5	3	19	14	65

* In this table all the observed attacks are included.

† 2 cases with same type both attacks.

‡ One of these cases had the same type during both attacks.

Location of the Pulmonary Lesion. In Table 5 are shown the numbers of cases having various lobes of the lung involved during the first observed attack, and these are correlated with the location of the lesion during the recurrence. If due allowance is made for the small numbers with which we are dealing, it may be said that the various lobes were involved with the usual frequency during both the early attacks and during the recurrences. Furthermore, there was no constant correlation between the site of the initial involvement and that of the reinfection. Thus, among the 32 cases with right-sided involvement during the first attack and

among the 26 cases with the left-side involved in this attack, about the same proportion of cases involved the right and the left lung, respectively, during the recurrent attack. Bilateral lung involvement, however, was twice as frequent during the recurrence. The site of the original lesion was involved during the recurrence in 36 instances (56%). Three of the 7 cases having the same fixed pneumococcus type during 2 successive attacks showed more extensive involvement during the later attack, and in 5 of them the original site was again affected.

Mortality. The death rates in this series are considerably lower than those obtaining in the general run of cases.¹⁴ They are shown in Table 6. Survival, however, is not the only criterion which differentiates mild from severe infection. Other features may be compared, however, and these may reflect to some extent the character of the different attacks.

TABLE 6.—MORTALITY.

Age in first attack.	Number of cases.	Died in later attack.	Per cent. fatal.
29 or less	31	2	6.0
30 to 49	20	6	30.0
50 or over	6	3	50.0
Total	57	11	19.0
	Number of attacks.	Attacks fatal.	Per cent. fatal.
Specifically treated	26*	0	0
Not specifically treated	96	11	11.5
Total	122	11	9.0

* 15 received serum during the first attack and 11 during the recurrence.

Duration of Acute Disease and Mode of Termination. It is interesting to compare the duration of the acute disease and the mode of termination in the different non-fatal attacks. Crisis, for this purpose, is arbitrarily defined as a permanent drop in temperature to below 101° F. with coincident marked alleviation of acute symptoms within a period of 24 hours. A more prolonged subsidence of fever and symptoms is called lysis. In this connection, it is also worth noting the mode of termination of the earlier attacks and some other features in the 11 cases which later ended fatally. These comparisons are shown in Table 4. In general, the successive attacks were quite similar in each individual as regards duration of the acute illness and mode of termination. In the fatal cases where definite complications did not account for such outcome the preceding attack was severe or otherwise complicated. In none of the fatal cases was the recurrence of the same pneumococcus type as the preceding attack.

Interval Between Attacks. (Table 7.) The shortest interval between attacks which were observed and were associated with

serologically identified pneumococci was 4 weeks, the longest interval was 11 years and 8 months, and the average was about 4 years. Of 19 cases recurring within a year, 4 were of the same pneumococcus type. These were each treated with specific anti-serum in the first attack. The second attack in these cases occurred 4 weeks, 6 weeks, 7 months and 9 months later, respectively. The average interval between attacks that were of the same pneumococcus type was 28 months.

TABLE 7.—INTERVAL BETWEEN ATTACKS OF PNEUMOCOCCUS PNEUMONIA.

Interval.	Number of cases.	Number with same type.*
Less than 2 months	5	2†
2 to 6 months	6	0
7 to 12 months	8	2‡
1 to 3 years	12	1
3 to 5 years	10	1
5 to 10 years	10	1
10 or more years	9	0
Total	60	7

* Excluding cases with Group IV on successive occasions.

† Both serum treated Type I cases, interval of 4 and 6 weeks, respectively.

‡ Both Type II cases, interval of 7 and 9 months, respectively; each serum treated during first attack.

Average interval between attacks in all cases—approximately 4 years.

Average interval between attacks due to same type—2½ years.

TABLE 8.—COMPARISON OF TYPES OF PNEUMOCOCCI RECOVERED DURING EARLY ATTACK AND DURING RECURRENCE.*

Type at first observed attack.	Type during recurrence.				Total (first attack).	Distribution per cent (first attack).
	I.	II.	III.	Others.		
I	4 ²	5 ²	3	8 ⁴	20 ⁸	33
II	5 ²	2 ²	1	4 ¹	12 ⁵	20
III	3	1	1	1	6	10
Others	7 ²	2	1	12	22 ²	37
Total (recurrence)	19	10	6	25	60	100
Per cent distribution (recurrence)	32	17	10	42	100

* Exponents represent the number of cases receiving specific serum during earlier attack.

Type II atypical included in Group IV.

Pneumococcus Types. The numbers and percentages of cases from which the various types of pneumococci were obtained during the early and the succeeding attacks are correlated in Table 8. When due allowance is made for the small numbers concerned, the distribution of cases among the various types during the early

attacks and during the recurrences is very similar to that found in any large series of cases of pneumococcus pneumonias. There was obviously no correlation between the types obtained during the different attacks. For example, the 20 cases with Type I pneumococci during the first attack had about the usual distribution of types during the succeeding pneumonia and, conversely, the 19 patients having Type I pneumococci in the later attack were similarly distributed among the different types during the first attack. The same was true for the other types.

The same type was isolated during the later attack in 4 of 13 cases in which homologous type antiserum had been given for a previous attack. It will be noted from Tables 1 and 2 that in 3 of these 4 treated cases (Cases 13, 27 and 36) the original lobe was involved during the recurrence.

Only a small proportion of the Group IV pneumococci in the present series were definitely classified according to the new serologic types of Cooper.⁷ In 5 of the 12 cases, however, in which pneumococcus types other than I, II or III were obtained during successive attacks, the finding of an atypical Type II, Type VIII (atypical III) or absence of agglutination for the original type indicated that the two attacks were probably associated with different types. Other organisms, chiefly hemolytic streptococci and influenza bacilli, were isolated in some instances in addition to the pneumococcus.

Bacteremia. In most of the cases in this series blood cultures were made on one or more occasions during each acute attack. Positive cultures were obtained in 9 of the 47 cases (19%) in which cultures were made during the first attack. In the latter attack 6 of 52 cases (12%) yielded positive blood cultures, and 3 of these 6 cases ended fatally. Only 1 patient had a positive blood culture during successive attacks, the latter one proving fatal. In most large series of cases bacteremia is usually demonstrated in about 30% of cases.^{14a}

Specific Therapy. Some kind of specific antipneumococcus serum was used in the treatment of 26 attacks in this series. (See Tables 1, 2, 3 and 7.) In 15 cases the serum was given during the first attack, and these alone are of interest for the purpose at hand. These 15 cases fall into 3 groups. In the first group are 7 patients in whom the recurrence was associated with a pneumococcus of a type not contained in the antibody administered. In the second group are 4 patients who were given a polyvalent antibody for the first attack and who had a recurrence with a pneumococcus type included in this antibody but different from the type causing the original infection. In the third group are 4 patients receiving homologous antiserum and having recurrences with the same type of pneumococcus. Cases 3 and 13 received homologous antiserum for a

Type I infection and had a recurrence with the same type 4 and 6 weeks later, respectively; and Cases 27 and 30 each had Type II pneumonia, were given concentrated Type I and Type II antibodies (Felton) during the height of the disease and had recurrences with the same type 9 and 7 months later, respectively. The pulmonary lesion in Cases 13, 27 and 30 was somewhat more extensive during the recurrence, but the site of the original attack was also affected during the recurrence. In Case 3 the later attack involved a different lobe.

Immunity Reaction. Data concerning antibodies are available in 7 of the patients, including 4 who were treated with serum during the first attack. All had antibodies for the homologous type after each attack. Only 1 patient (Case 29) had antibodies for the original type of pneumococcus at the time of the recurrence, 1 year later. In Case 27 the homologous Type II antibodies disappeared within 2 weeks after serum treatment, and pneumonia due to the same type recurred in 9 months. In Case 16 there was a spontaneous recovery with a high titer of homologous (Type I) antibody persisting for several months, but pneumonia recurred with the same type about 3 years later.

Comment. The cases in this study were included, after a search of more than 5000 "typed" cases in two large hospitals, because they were the only ones found to satisfy the criteria set down. No attempt was made to determine the exact incidence of previous infections in the entire group of pneumonia patients in these clinics because it was felt that the histories could not always be considered reliable and no satisfactory information could be obtained regarding the details of such illness, especially in regard to etiology. It is interesting to note, however, that among 1000 consecutive "typed" cases of pneumococcus pneumonia in which data on this point were recorded, a history of one or more attacks before admission was noted in 16.5%. Indeed, in the present series, 6 cases were observed in 3 attacks, 1 in 4 attacks and 13 (23%) gave a history of one or more attacks of pneumonia previous to the first entry to the hospital. These figures correspond to those recorded by other writers.¹ A review of the case histories of 1000 consecutive medical patients treated for diseases other than pneumonia, however, revealed that 14% of these individuals gave a history of one or more attacks of pneumonia prior to entry.

With respect to the character of the different attacks, most of the data presented seems to indicate that, in general, the successive attacks, considered as a group, were very similar. The duration of the disease and mode of termination were similar. Bacteremia was nearly as frequent, and the distribution of the sites of the lesion and of the different pneumococcus types was very similar in the early and in the later attacks. Among the fatal cases, either there

was some other important contributing factor in the fatal attack or the preceding attack was also unusually severe.

The group of later infections did differ, however, in two important respects: (1) Bilateral involvement was twice as frequent; and (2) the instances of bronchopneumonia occurred chiefly in the last attack. With respect to the former it may be noted that in 14 of the 18 instances where there was more extensive involvement in the later attack, the site of the original infection was again involved. This, and the fact that in 16 other instances the same lobe was involved in successive attacks, indicates that there is certainly no increase in local resistance.

With regard to the instances of "atypical" or bronchopneumonia, two points may be mentioned which suggest that this type of lesion may indicate a greater susceptibility during the later disease. First, the types of pneumonia generally associated with such lesions are frequently avirulent for animals, in contrast with the highly virulent pneumococci, usually Types I and II, associated with typical lobar pneumonia.³ In a recent study^{14c} it was further shown that where the same type of pneumococcus causes both lobar pneumonia and bronchopneumonia, the cases with the latter type of involvement are more often secondary to other diseases and have a much higher fatality rate, presumably indicating a lower resistance brought about by the primary disease.

In only 4 instances was there any evidence suggesting that persistence of the original virulent organisms may have accounted for the recurrence. These were the 4 cases in which reinfection with the same type occurred within a year. In 1 of these cases, however, careful study of the sputum on several occasions after the first few days of the original infection failed to reveal the Type II organism originally in the sputum and blood and which was again recovered from the sputum at the time of the second attack.

That the specific humoral immunity resulting from reinfection or immunization with pneumococci is of brief duration is well recognized. Occasional instances of persistent antibodies for a year or more, such as was noted in Case 29, have been observed before.¹⁵ The measures of immunity usually employed, however, are not very delicate, and the interpretation of these immune reactions in terms of actual susceptibility in man is not clear. In the only case in this series where immunity to any type was demonstrated early in the disease, the infection was caused by another type. The demonstration of circulating type-specific antibodies, or even of tissue immunity, if the specific skin reactions may be interpreted as such, does not preclude later infection with the same pneumococcus type. Nor do the present data indicate that specific serum treatment seriously alters the future susceptibility to the same type,

although specific antibodies can be demonstrated for shorter periods in such cases as compared with those recovering spontaneously.¹⁶

Summary and Conclusions. In this paper is presented a study of 57 cases having recurrent attacks of pneumonia associated in each instance with serologically identified pneumococci.

An analysis of the major features of the early attacks and of the recurrence fails to indicate any marked change in the local or type-specific susceptibility.

The distribution of types of pneumococci and of the sites of the pulmonary lesion, both in the early and the late attacks, was very similar to that usually observed in pneumococcus pneumonia.

A larger number of cases had more extensive and "atypical" lesions during the recurrent attack.

Specific serum therapy in the first attack in general had no marked effect on the character of the recurrence. Early recurrences with the same type, however, are more frequent among the serum-treated cases.

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THE CYTOLOGY OF PLEURAL EFFUSIONS IN PNEUMONIA STUDIED WITH A SUPRAVITAL TECHNIQUE.*

By T. F. McNAIR SCOTT, M.R.C.P. (LONDON),
INSTRUCTOR IN PEDIATRICS, HARRIET LANE HOME, JOHNS HOPKINS HOSPITAL,
BALTIMORE, MD.,

AND

MAXWELL FINLAND, M.D.,
FRANCIS WELD PEABODY FELLOW IN MEDICINE, HARVARD MEDICAL SCHOOL, AND
ASSISTANT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY
HOSPITAL, BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services
(Harvard), Boston City Hospital and the Department of Medicine, Harvard
Medical School.)

THE observations of Gay and his associates¹⁻⁵ have indicated that the type of cell present in the pleural exudate, experimentally induced in rabbits, has a determining influence on the establishment and the course of local streptococcic infections, and possibly, also, on those with the pneumococcus.⁶ In the course of pneumococcic pneumonia in man, there is always some pleural reaction, and actual effusion may be present in a large percentage of cases. In some instances, such an effusion remains sterile and is absorbed; in others, it becomes infected and may require intervention. A study of such effusions, at various stages of pneumonia, was undertaken in the hope that information might be obtained in regard to their probable course and outcome. The immunologic characteristics of such fluids have already been reported by one of us.⁷ The present study concerns the cytology of such fluids as revealed by a supravital technique which gives a clear differentiation of the cells and also yields information regarding their viability and activity.

The presence of pleural effusion in pneumonia has long been recognized.⁸⁻¹⁰ Its frequency has been indicated by many observers,¹¹⁻¹³ some of whom differentiated between the benign serofibrinous fluids and the serious purulent type.¹⁴⁻¹⁹ Studies of the cells in such fluids were made by Quincke²⁰ and by Ehrlich,²¹ the latter using stained preparations. Widal and his associates,^{22,23} however, were the first to indicate the diagnostic significance of the cytological formula. They recognized the presence of "macrophages" and lymphocytes late in pneumonic effusions which remained sterile. Similar observations were made in occasional cases by Dopter,²⁴ and by other writers^{25,26} in the pneumonias of infants by Ylppö²⁷ and in an effusion of typhoid fever by Pepper.²⁸ Eosinophilia, up to 65%, has been noted late in pneumonic effusions.²⁹⁻³² Studies of exudates, including occasional pneumonic pleural fluids, with the aid of vital stains have been reported recently by Uijeyonahara³³ who used soda carmin and by Hickling³⁴ who used neutral red.

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Materials and Methods. A total of 53 fluids, 32 sterile and 21 infected, were obtained from 32 patients with clinical and roentgenographic evidence of lobar pneumonia. Pneumococci were cultured from the sputum or blood of each patient. With one exception (Case 25, in which the fluid became secondarily infected during an hemolytic streptococcus septicemia that complicated convalescence), the same type of pneumococcus was recovered from each infected fluid as was originally obtained from the sputum or blood. Agglutinating sera, Types I to XX (Cooper³⁵) were used to type the pneumococci. Specific serum (Felton) was used in the treatment of 9 of the patients. Novocain in a 1 to 2% solution was used for local anesthesia. The hydrogen-ion concentration was obtained with the use of indicators by comparing with standard buffer solutions (Clark³⁶).

The fluids varied in appearance from clear and straw-colored fluids which clotted readily, and which were called "sero-fibrinous" to hemorrhagic fluids and frank pus. In the latter there was little doubt as to the nature of the fluid, but in those which were seropurulent it was impossible to tell grossly whether or not the fluid was infected.

A total leukocyte count and a differential count of 100 to 400 cells was made as soon as possible after the fluid was withdrawn. In some instances accurate total counts were not made due to the rapid clotting of the fluids. The supravital technique employed was that described by Forkner³⁷ which is a modification of the methods of Simpson³⁸ and Sabin³⁹ and their associates. It consists essentially in a study of the reaction of the various cells to two anilin dyes, neutral red and Janus green, which preserve their activity and undistorted morphology. Neutral red is an indicator which stains the specific granules and vacuoles different shades from red to yellow depending on whether they are acid or alkaline. Thus, the granules of eosinophils, which are essentially alkaline, stain a yellowish color, while those of a basophil, which are essentially acid, stain bright red. Janus green, in the concentration used, is a specific stain for mitochondria. These vary with different cells and also with the age of the cells, being coarse in lymphocytes and fine in monocytes and tending to be more numerous in the more immature cells. Essentially the cells in these fluids were similar to those described in the blood or other tissues by the originator and the elaborators of the method.^{38,39} Some of the characteristics of the cells, especially as they differ from those found in blood, will be discussed below. Examples of the appearance of most of the cell types encountered are shown in Plate I.

Cytologic Findings. The significant data relating to each of the patients and to the fluids are given in Table 1. These findings will be summarized in connection with the discussion of the various types of cells encountered.

Polymorphonuclear Neutrophils. Four different forms were encountered: (1) active; (2) rounded; (3) degenerating and (4) non-motile. The *active* forms were motile and had yellowish specific granules similar to those found in the cell of blood. They differed from the latter in 3 respects. (1) The "specific granules" stained poorly in many instances. (2) Red "segregation granules" were noted. These were, in reality, vacuoles filled with acid staining products of metabolism and were similar to the ones noted by Sabin³⁹ in the blood neutrophils in a case of pneumonia. (3) Large numbers of "refractile globules" accumulated in the cytoplasm. Such heavily loaded cells moved sluggishly. While these cytoplasmic changes may represent increased phagocytic activity, they probably also

indicate cell damage, since similar refractile globules appear in dead leukocytes. The granules may be due to the inability of the cells to absorb some of the ingested materials but more probably indicate beginning degeneration. The *rounded* forms were similar to those found in blood. They probably represent a state of temporary or permanent inactivity. The *degenerating* and *dead* forms showed a characteristic reaction to neutral red. The former, if still living when the stain was applied, took up the dye very quickly, the nucleus staining a diffuse red, indicating that the cell died soon after being stained. The dead cells were rounded and failed to stain. Their cytoplasm showed a few refractile granules and the nucleus had a ground-glass appearance and formed a round swollen mass in the center of the cell. The *non-motile* cells appeared the same as similar cells in blood, but they were seen only rarely. Hickling failed to observe them in any of his cases. According to Sabin³⁹ they represent cells about to die a natural death. Their rare appearance in these fluids may depend on their lack of motility. All of these forms were seen in varying proportions in the majority of the effusions studied.

The predominance of neutrophilic polymorphonuclear cells in pleural fluids accompanying acute infections has been noted by all observers.²²⁻²⁸ In the present cases these cells constituted from 80 to 100% of leukocytes in the early uninfected fluids and practically 100% in all the infected effusions. In fluids which remained uninfected, the proportion of these cells tended to fall rapidly, so that after the 8th day they constituted less than 60% of the cells in almost every case; whereas, in those which later became infected they remained at, or rapidly reached, 100% (Fig. 1). In infected fluids the majority of these cells lost their motility and assumed first the rounded, then the degenerating and finally the dead form.

Experimentally, the rounded forms and the faintly staining active forms could be induced in normal blood by mixing it with equal parts of 2% novocain solution before staining. The presence of novocain, however, probably did not account for the findings in the fluids, inasmuch as only small amounts of novocain in separate syringes were used for anesthesia and care was taken not to introduce any into the pleural cavity.

Eosinophils. These were very similar in appearance to blood eosinophils. They were less motile than the neutrophils and con-

LEGEND FOR PLATE I.

Pencil drawing of cells from pleural fluids as they appear supravitality stained with neutral red and Janus green. ($\times 1400$.) 1, rounded polymorphonuclear neutrophil; 2, active polymorphonuclear neutrophils; 3, active polymorphonuclear neutrophil with many refractile granules; 4, mesothelial cell; 5, small lymphocyte; 6, monocytes; 7, macrophage, with many red stained vacuoles; 8, macrophage with ingested polymorphonuclear neutrophil but only few vacuoles; 9, erythrocytes.

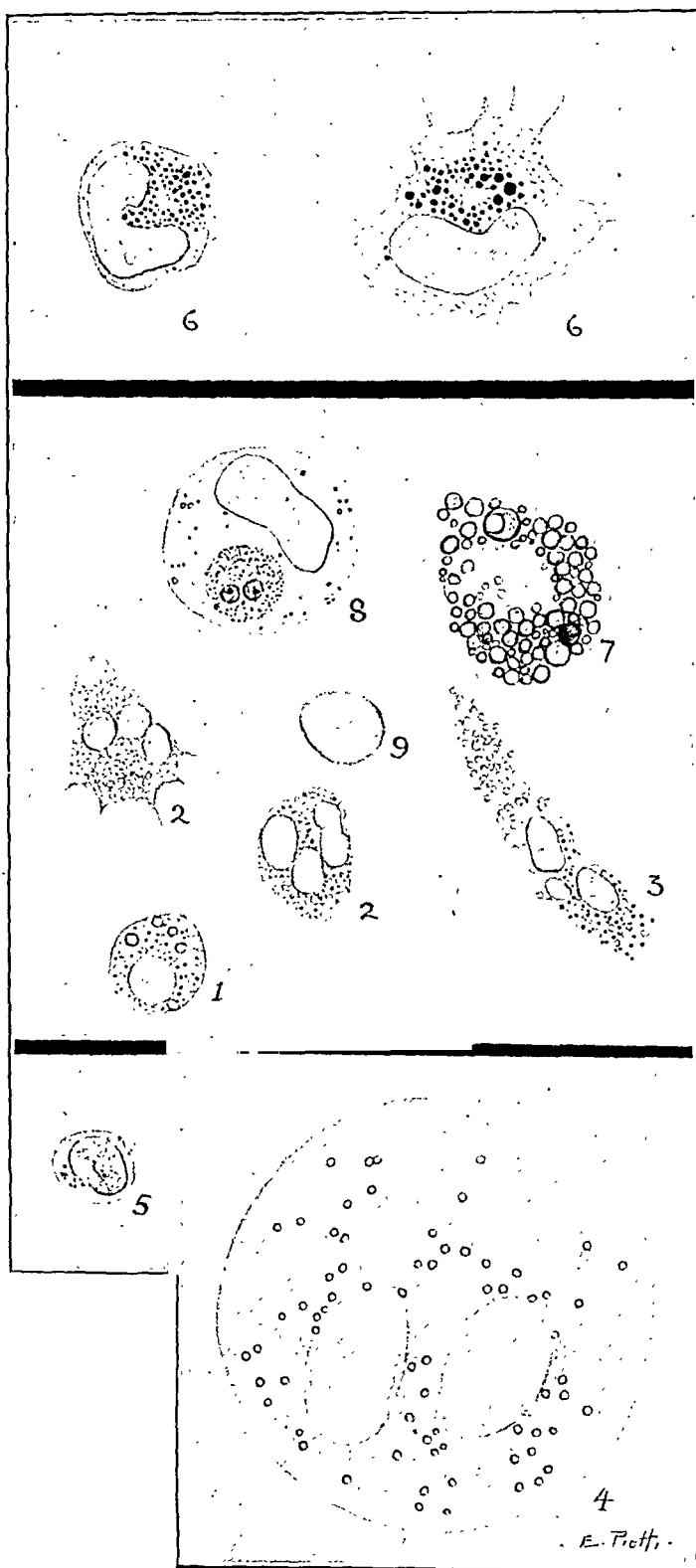


PLATE I.

INFECTED FLUIDS.

Patients receiving no serum.				INFECTED FLUIDS.									
					100 0	Many pneumococci seen.	24.6	50.0	80.0	0	16.0	0	
21	I	D. 4	Ser. Fib.	7.2	10.0	0	0	0	0	0	0	0	2.0
22	0	Op. 18	Fib. Pur.	...	1.5	0	0	0	0	0	0	0	+
23	IX	Op. 6	Pur.	7.2
24	III	Op. 8	Ser. Fib.	7.8	6.3	87.0	3.0	1.0	94.0	0	2.0	2.0	0
25	I	Op. 10	Ser. Pur.	...	9.6
26	I	D. 8	Sang.	...	18.5	86.0	0	0	86.0	0	1.0	2.0	1.0
27	I	Op. 17	Ser. Pur.	6.4	2.2	80.0	3.0	9.0	93.0	0	1.0	2.0	3.0
28	II	D. 19	Pur.	7.6	...	10.0	0	83.0	0	93.0	0	5.0	7.0
29	I	Op. 19	Pur.	6.4	0
30	Pur.	5.6	594.0	+
31	Pur.	5.6	?	+

Patients treated with specific serum.

					95.0	0	5.0	0	100.0	0	0	0	0	0	0	0	0	0	0
30	I	Op. 19	Ser. Fib.	7.2	9.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31	Ser. Fib.	7.0	40.7	84.0	0	15.5	0	99.5	0	0	0	0	0	0	0	0	0
32	Fib. Pur.	6.3	41.6
33	Pur.	6.3	291.0

STERILE FLUIDS LATER BECOMING INFECTED.

					48.0	1.0	3.0	0	47.0	3.0	7.0	13.0	28.0	41.0	1.0	1.0	1.0	1.0	1.0
31	II	Op. 31	Ser. Sang.	8.0	30.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
32	Ser. Fib.	8.0	19.2	19.5	0	0.5	0	20.0	2.5	37.5	26.0	11.0	37.0	0	3.0	0	0
33	Pur.	7.2	...	29.0	0	65.0	0	94.0	0	0	0	3.0	3.0	6.0	0	0	0
34	Pur.	5.4
35	I	Op. 27	Ser. Fib.	8.0	2.5	34.0	0	0	34.0	0	16.0	22.0	24.0	46.0	2.0	2.0	2.0	2.0	2.0
36	Pur.	6.4

NOTES.—The following are not included in the tabulation:
Polymorphonuclear leucocytes: 1.0% in Case 51.
Mycocytes: 4.0% in Case 3 on the 8th day; 6.0% in Case 20.
Foreign Body Giant Cells: 1.0% in Cases 16 and 20.
 Case 4.—Fluid was studied before and after serum was given.
 Case 31 was treated with specific serum and developed β -hemolytic streptococcus septicemia on the 25th day. First 2 fluids were sterile; from the last 2 hemolytic streptococci were grown.
 Case 32 was treated non-specifically with normal horse serum; first fluid was sterile; from second Type I pneumococci were grown.

tained numerous large copper-colored granules. They were encountered, in significant numbers (12% or more), in the fluids from 3 cases. These were all sterile effusions obtained after the middle of the 3d week of the disease, the highest percentage (71%) being noted on the 27th day and later in Case 15.

Little is known about the function of eosinophils. Bunting⁴⁰ considers the breakdown products of lymphocytes specifically chemotactic for eosinophils, thus explaining their occurrence in the lymph nodes in Hodgkin's disease. Schwartz,²⁹ on the basis of the association of eosinophilia and protein sensitiveness, suggests that the split products of protein absorption, such as occur in pleural fluids, are eosinotactic. The data for cases of pleural eosinophilia associated with pneumonia²⁹⁻³² as well as the experimental evidence

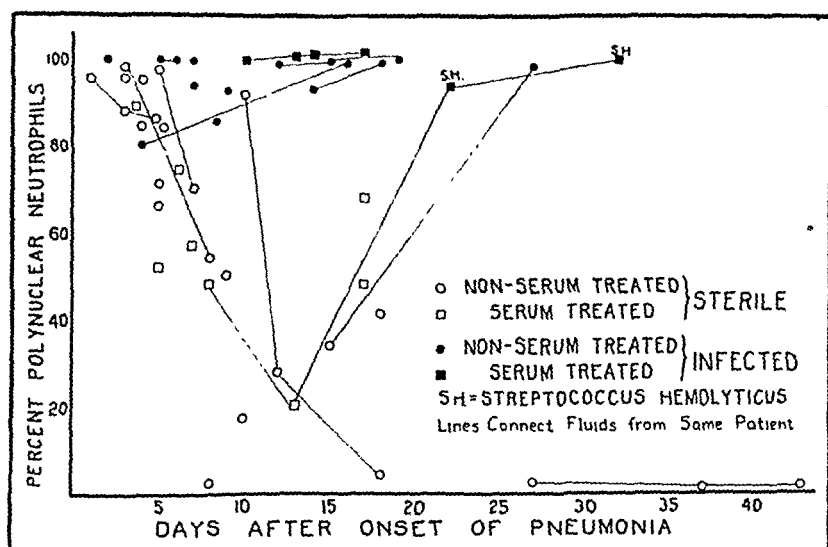


FIG. 1.—Relation of polymorphonuclear neutrophils in pneumonic pleural fluids to the course of the disease.

of Cunningham⁴¹ indicate that eosinophilia appears only in fluids of relatively long standing. This corresponds with the present findings. There was no particular correlation of the high eosinophil counts with the finding of numerous erythrocytes, as suggested by Cunningham⁴¹ or with high percentage of lymphocytes as indicated by Bunting.⁴⁰ Only moderate blood eosinophilia has been found in the reported cases of pleural eosinophilia,³⁰ and this was also the experience in Case 15 as indicated in Table 2.

TABLE 2.—EOSINOPHIL PERCENTAGES IN CASE 15.

Day of disease.	Per cent eosinophils.	
	Pleural fluid.	Blood.
27	71	10
37	70	12
43	57	4

Monocytes as they appeared in the fluids studied were, for the most part, identical with those in the blood. The cytoplasm tended to form sharp pointed pseudopods and contained salmon-pink granules and fine mitochondria. The nucleus was round or indented. Atypical forms were observed, however, in which the cytoplasm was edematous and billowed out widely around the nucleus. These forms probably represent early degeneration since similar forms were observed in the blood and novocain mixtures previously mentioned.

Macrophages (Clasmatocytes). These cells which were described in detail by Sabin⁴² were large cells, each with single round nucleus containing nucleoli and with cytoplasm containing ingested erythrocytes, other particulate matter and few or numerous vacuoles of varying color. These cells often occurred in clumps of 4 or more, usually associated with monocytes or other cells.

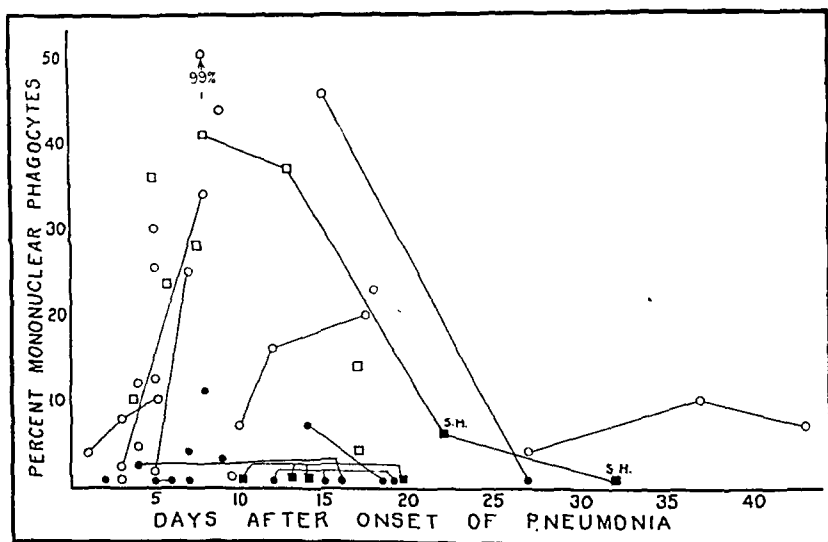


FIG. 2.—Relation of mononuclear phagocytes in pneumonic pleural fluids to the course of the disease.

Forkner⁴³ and other authors consider that, under stimulation, monocytes can become macrophages. In this study, the monocytes were not infrequently observed to become filled with a large number of vacuoles, making them morphologically indistinguishable from macrophages. These 2 types of closely related cells are, for convenience, grouped together as *mononuclear phagocytes*. As will be seen from Fig. 2, these cells behaved in the reverse manner to the polymorphonuclear neutrophils. Early in the disease they were few or absent in all cases. In sterile fluids the percentage rose rapidly. In fluids infected early they failed to appear, and in those later becoming infected they rapidly disappeared.

The rôle of these phagocytic cells is not entirely clear. Ylppö²⁷ attributes to them the fact that the most serous effusions fail to become purulent. Petzetakis⁴⁴ found that serous effusions accompanying simple bronchitis in children have a high percentage of these cells early in the disease. This may account for the absence of empyema in such cases, the mononuclear phagocytes acting as a protective barrier. Gay and his coworkers¹⁻⁵ showed that the clasmatocyte serves to protect against experimental streptococcic infections and, possibly, also against pneumococcic infections⁶ in the pleura of rabbits. In the present series only 3 of the 20 cases with a total of over 10% of combined monocytes and macrophages ever became infected.

Lymphocytes. These were mostly small cells resembling the small lymphocytes of the blood, although a few cells of intermediate size were usually present. Significant numbers (over 10%) were observed in 9 cases, one of which had infected fluid at the time and 2 others in which the fluid later became infected. With one exception (Case 22), more than 10% lymphocytes were observed late in the disease and after the crisis. Their appearance followed several days after the rise in mononuclear phagocytes.

Some defensive rôle is generally assigned to lymphocytes in certain infectious diseases, particularly in tuberculosis, where it is felt that an increase in these cells at the expense of the monocytes indicates an increase in the patient's resistance. Reich and Reich⁴⁵ found, during convalescence from severe infections, a shift to the left of the lymphocytic hemogram, similar to that which is commonly found with the polymorphonuclear cells during other infections. In the present series of cases there appears to be some relation between the lymphocytes and the resolution of the inflammatory process in the lungs, the appearance of these cells following, in sequence, after the height of the increase in the polymorphonuclear and in mononuclear phagocytic cells. They could not be considered entirely protective inasmuch as one-third of the fluids with over 10% lymphocytes became infected.

Mesothelial Cells. These were very large cells containing 1 or 2 nuclei characterized by a well-defined nuclear membrane and nucleoli. The cytoplasm was usually unstained and contained many small unstained refractile globules. Some contained, in addition, a number of red vacuoles of varying size (Plate I). Cunningham⁴¹ described similar vacuoles in mesothelial cells from animals with marked peritoneal irritation and considered them a sign of degeneration. This author and Sabin⁴² consider these mesothelial cells to be fully differentiated cells which line the serous surfaces but have no phagocytic properties. They were seen, in the present series, fairly constantly as small numbers of desquamated cells. No transitional forms were noted and none of the cells were seen to exhibit phagocytosis.

In addition to the cells described above, occasional *myelocytes*, *foreign body giant cells* and *polymorphonuclear basophils* were noted (Table 1, footnote). The latter occurred in Case 15 in association with the increase in eosinophils. A similar basophilia was noted by Bayne-Jones in his cases of pleural eosinophilia.³⁰

Summary. A supravital technique was used to study the cytology of 53 pleural fluids from 32 patients with pneumococcus lobar pneumonia. The cell types encountered are described. Their occurrence and frequency are correlated with the outcome of the effusion and the course of the pneumonia.

The cellular content of the infected fluids consisted almost exclusively of polymorphonuclear neutrophils in various stages of degeneration. In uninfected fluids the predominating cells, in the beginning, were active polymorphonuclear neutrophils, but these decreased in number during the first week at which time monocytes and macrophages appeared in the fluid. Later in the disease, after crisis had taken place, lymphocytes began to appear in these sterile fluids.

Moderate to marked eosinophilia was noted in 3 cases. This occurred during the 3d week, or later, after the onset of the pneumonia.

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THE OCCURRENCE OF MYELOCYTES IN THE PERIPHERAL BLOOD IN LOBAR PNEUMONIA.

By D. J. STEPHENS, M.D.,

INSTRUCTOR IN MEDICINE, THE UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY; ASSISTANT PHYSICIAN, STRONG MEMORIAL HOSPITAL, ROCHESTER, N. Y.

(From the Department of Medicine, The University of Rochester School of Medicine and Dentistry and the Medical Service of the Strong Memorial Hospital and the Rochester Municipal Hospital.)

THE voluminous literature on the blood findings in pneumonia contains but few references to the occurrence of myelocytes in the peripheral blood. In 1898 Turk¹ found that "mononuclear neutrophilic leukocytes" occurred in small numbers during the acute stage of the disease, in larger numbers at the time of the crisis and immediately thereafter, and similar observations have been made by Gaitskell,² Schindler³ and Hittmaier.⁴ In 26 of 36 cases of lobar pneumonia reported by these 4 authors, significant numbers of myelocytes were noted in the peripheral blood; the maximum myelocyte response occurred during the week following the crisis and varied in magnitude from 0.2 to 9.2% of the total leukocytes. In the available reports of others who have studied the blood in lobar pneumonia, myelocytes may have been included with stab forms under the heading of "immature neutrophils" but have not been mentioned specifically. In many of the patients described in the literature, hematologic observations have not been carried beyond the febrile period of the disease.

The investigation here reported was undertaken following the observation of a myelocytosis of considerable degree in the peripheral blood of a patient (R. P.) recovering from lobar pneumonia. The leukocyte response of 42 additional patients was studied in detail during the acute febrile and convalescent periods of the disease, using both fixed and supravital stained preparations. In the majority, myelocytes were noted at some time during the period of observation. Especially noteworthy was the consistent appearance of a shower of myelocytes in the peripheral blood of convalescent patients during the immediate postfebrile period.

Method. Total white blood cell and differential counts were done daily during the febrile period. In patients who recovered, observations were continued at daily intervals for several days after the temperature became normal, somewhat less frequently during the latter period of convalescence. A total of 574 fixed and supravital preparations were studied. All of the differential counts (200 cells) were done by the author. In the fixed smears, using cover slips, Wright's stain, buffered dilution, Schilling's classification⁵ was used. The supravital preparations were stained and studied by Sabin's⁶ and Simpson's⁷ method. In fixed smears, occasional mononuclear, granular cells were encountered, which were difficult to classify; such doubtful cells were uniformly classed as monocytes rather than as myelocytes or juveniles (late myelocytes). In the supravital preparations, the myelocytes observed were almost invariably the "C" type (Sabin). As a rule, when myelocytes were encountered in the peripheral blood, both fixed and supravital preparations were studied.

Except as to the myelocyte, our observations of the leukocytic response in lobar pneumonia were in accord with recent reports and may be briefly summarized. In fatal cases, as well as in those patients who recovered, the total white blood cell counts varied widely from case to case, and during the disease in the same patient. A valuable index of prognosis during the febrile period of the disease was to be found in the percentage of "stab" neutrophils from day to day. A significant shift in the proportion of neutrophilic elements often preceded clinical manifestations of change by many hours. In 12 of 13 fatal cases there was a definite increase in single lobed neutrophils before death (Chart I). In patients who were to recover, the percentage of stab cells often began to fall hours or days before the decrease in temperature or clinical evidence of improvement, and usually dropped to an approximately normal level within a day or two after defervescence (Chart II). In the great majority of instances, spread of the pneumonic process or the development of a complication was accompanied by an increase or persistent elevation of the stab percentage (Chart III). Eosinophils were absent, or rarely present in extremely small numbers, throughout the febrile period in both fatal and recovered cases; they reappeared in small numbers at the time of crisis or lysis, and increased during convalescence. Convalescence eosinophilia was occasionally observed. The lymphocytes were uniformly decreased during the

febrile stage and gradually increased during the recovery period. A monocytosis at the time of defervescence or shortly thereafter,

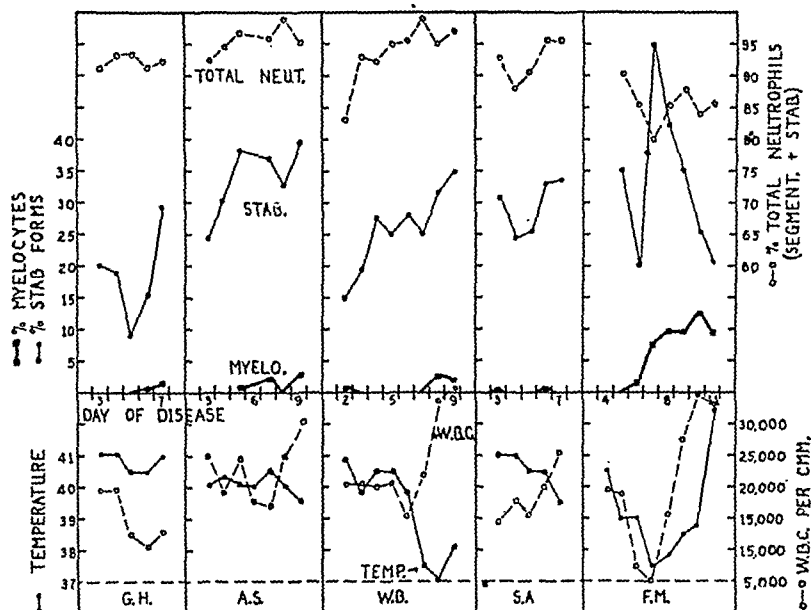


CHART I.—Neutrophilic leukocyte response of fatal cases.

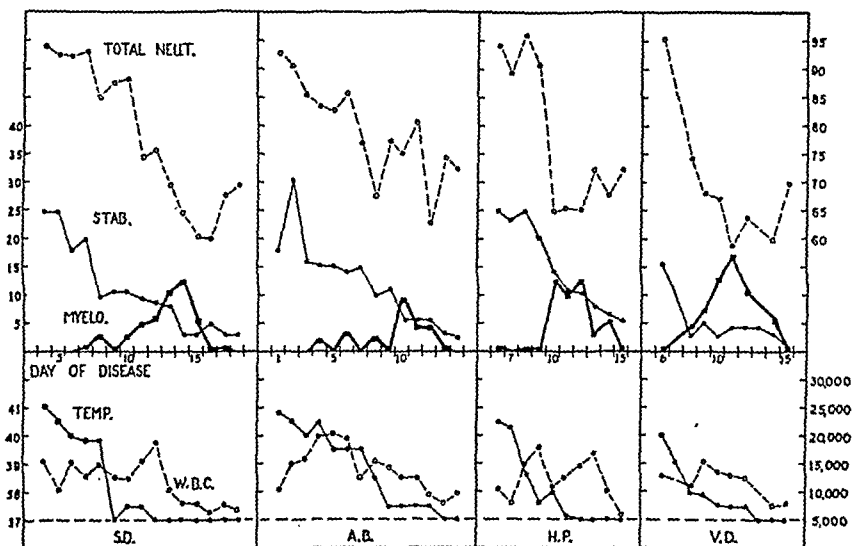


CHART II.—Neutrophilic leukocyte response of recovered patients.

recently emphasized by Hickling,⁸ was observed in 13 of the 30 recovered patients. In 5 of these the monocytes comprised 10, 10, 10, 12 and 16% of the total leukocytes.

In the great majority of patients, small numbers of myelocytes were found in the peripheral blood during the early, febrile period of the illness. They were most frequently observed after the 3d or 4th day of the disease and were rarely present in excess of 1 or 2% of the total leukocytes. The degree and frequency of peripheral myelocytosis during the acute stage of the disease was approximately the same in those patients who were to recover as in those who died (Charts I and II).

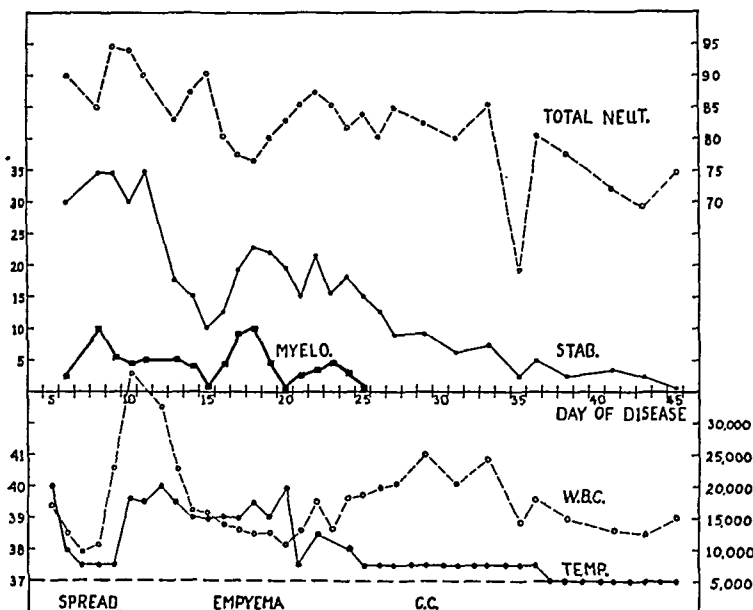


CHART III.—Neutrophilic leukocyte response in lobar pneumonia complicated by empyema.

In 12 of the 13 fatal cases, myelocytes were observed in the peripheral blood at some time during the period of observation. In 11 of these, the myelocyte increase was not striking, ranging from 1 to 3% of the total leukocytes. However, 1 patient (F. M.) exhibited a terminal increase in myelocytes to 12%. During the 5th and 6th day of the disease there was an apparent crisis, with drop in temperature, total white blood cells and stab neutrophils, coinciding with clinical evidence of improvement. On the 7th day there was an abrupt increase in the percentage of stab cells from 21 to 50% with the appearance of 7.5% of myelocytes (regenerative shift to the left of Schilling) although the temperature and total white blood cell count remained low. The next day there was evidence of spread of the pneumonic process. During the subsequent 3 days there was a progressive decrease in the percentage of stab cells, but a steady increase in myelocytes, total leukocytes, temperature and

clinical evidences of toxicity. The patient died on the 11th day with clinical and pathologic evidence of widespread pneumonia, empyema and pneumonococcic meningitis. Of the fatal cases, this was the only one of our small series who exhibited a definite "regenerative shift to the left," the prognostic significance of which has been stressed by Schilling. This was also the only patient in whom a terminal increase in the percentage of stab neutrophils was not observed. The temperature changes and the blood findings of this patient and of 4 other representative fatal cases are shown in Chart I. Eosinophils, basophils, lymphocytes and monocytes are omitted from the charts.

TABLE 1.—HEMOGRAM ON THE DAY OF MAXIMUM MYELOCYTE RESPONSE OF EACH OF 30 PATIENTS WHO RECOVERED FROM LOBAR PNEUMONIA.

Patient.	Day of disease.	Temperature.	Total W B C.	% Basophils.	% Eosinophils.	% Myelocytes	% Juveniles	% Stab. forms.	% Segmented forms.	% Lymphocytes.	% Monocytes.	% Myelocytes supra-vital	Remarks.
R. P.	12	37.2	11,850	0.5	1.0	12.5	7.5	11.5	42.5	23.0	1.0	16.5	Crisis 8 D.
V. D.	11	37.5	13,150	0.0	1.0	16.0	1.0	4.5	53.5	19.0	5.0	15.0	Crisis 6 D.
L. P.	10	39.6	43,600	0.0	2.5	12.5	3.0	14.0	59.5	7.0	1.5	11.5	Empyema.
G. B.	10	37.0	14,500	0.0	1.0	10.0	4.0	6.5	59.5	16.5	2.5	...	Crisis 8 D.
H. P.	10	38.0	11,200	0.0	0.5	9.0	3.5	14.0	53.0	18.0	1.0	13.0	Crisis 8 D.
S. D.	14	37.0	8,850	0.5	0.0	9.5	2.5	3.0	61.0	18.5	4.5	10.0	Crisis 9 D.
Ch. C.	14	37.5	13,600	0.5	3.0	8.5	2.5	4.5	56.0	17.5	2.5	8.0	Crisis 11 D.
C. C.	8	37.5	11,800	0.0	0.0	8.5	1.5	34.0	52.5	3.0	0.0	11.0	Empyema.
E. C.	7	38.2	19,800	0.0	0.0	7.5	1.5	8.0	67.0	12.5	3.5	8.0	Lysis 4-6 D.
G. C.	13	38.7	15,100	1.0	0.0	8.0	1.0	2.5	70.0	15.5	2.0	9.0	Empyema.
W. K.	10	37.5	10,700	0.0	1.0	8.5	0.5	4.5	48.0	34.0	3.0	9.0	Crisis 8 D.
L. R.	12	37.5	14,200	0.0	1.5	8.5	0.0	1.0	79.5	13.0	1.0	...	Crisis 7 D.
A. B.	10	37.6	13,300	0.0	0.0	6.5	1.5	6.5	69.0	6.5	8.5	5.0	Lysis 7-9 D.
A. T.	10	38.0	19,900	0.0	2.5	7.0	1.0	5.0	64.5	19.0	1.0	7.0	Lysis 7-10 D.
L. P.	11	37.5	20,800	0.5	0.5	7.5	0.0	1.5	72.5	14.0	3.5	8.5	Crisis 7 D.
W. K.	6	37.7	7,600	0.0	5.0	6.0	0.5	2.5	64.0	21.0	1.0	5.5	Crisis 3 D.
H. F.	10	38.0	14,000	0.0	1.0	5.0	1.0	6.0	73.0	11.5	2.5	6.5	Crisis 6 D.
P. G.	12	37.5	9,000	0.0	2.0	5.5	0.0	3.0	70.0	12.5	7.0	6.5	Lysis 7-10 D.
J. M.	?	39.2	26,000	0.0	0.5	5.0	0.0	8.0	77.0	4.0	4.5	...	Lysis.
V. K.	9	37.8	9,100	1.0	0.0	4.5	0.5	8.0	60.5	12.5	13.0	6.0	Lysis 5-7 D.
J. G.	15	37.5	11,250	1.0	2.0	4.5	0.5	4.0	68.5	14.5	5.0	4.5	Crisis 10 D.
G. F.	15	37.5	11,000	0.0	0.5	4.5	0.0	2.0	67.5	21.5	4.0	5.0	Crisis 11 D.
P. U.	10	37.3	7,800	0.5	1.0	3.5	0.5	2.0	66.0	26.0	0.5	...	Crisis 5 D.
P. W.	17	37.8	7,000	1.5	3.0	2.5	1.0	2.5	60.5	23.5	5.5	3.0	Lysis 3-6 D.
E. H.	7	37.5	8,400	0.0	4.5	2.5	0.0	1.5	61.5	25.5	3.5	3.5	Lysis 4-6 D.
W. R.	13	38.8	8,000	0.0	1.0	2.0	0.5	14.5	71.5	10.0	0.5	...	Lysis 8-13 D.
C. P.	8	37.3	5,250	0.5	0.5	2.5	0.0	1.0	77.5	16.0	2.0	1.5	Crisis 6 D.
N. T.	8	38.8	11,900	0.0	0.5	1.5	0.5	14.5	64.0	11.0	7.0	...	Crisis 4 D.
J. P.	5	37.5	7,350	0.0	6.0	1.0	0.0	7.0	58.0	20.0	7.0	...	Lysis 3-5 D.
F. R.	6	40.2	10,500	0.0	0.0	0.0	1.0	23.0	68.0	18.0	0.0	...	Lysis 8-14 D.

The most striking myelocyte response was observed in those patients who recovered. Although a mild myelocytosis was frequently observed during the febrile period, the maximum myelocytosis occurred after the acute manifestations of the disease had subsided. The temperature and hemogram on the day of the maximum myelocyte response in each instance are shown in Table 1. In two-thirds of the recovered patients, the myelocytes at their

maximum amounted to 5% or more of the total leukocytes; in almost one-third, to 10% or more; in 3 of them to more than 15%. The average myelocyte peak for the 30 cases was 7.5%. Of the 30 patients, 27 recovered without complications; in the majority of these the myelocyte peak was noted from 1 to 5 days after defervescence (Table 1). In 2 instances (N. T. and P. W.), the maximum myelocytosis occurred during serum sickness. In general, the myelocyte response was greater in those whose temperature fell by crisis than in those who recovered by lysis, but apparently it was not influenced by age, sex, or type of pneumococcus. Myelocytes usually appeared a day or two before the drop in temperature, attained a maximum 2 to 6 days later, and in most instances disappeared from the peripheral blood within a week. At the time of the maximum myelocyte response in uncomplicated cases, the temperature and percentage of stab neutrophils had fallen to an approximately normal level; frequently, however, there was still a definite elevation of the total leukocyte count. Chart II shows 4 typical neutrophilic responses.

In 3 cases complicated by empyema a marked increase in myelocytes occurred at about the same stage of the disease as in uncomplicated pneumonia, but persisted for a longer period of time. In patient C. C. (Chart III) a secondary myelocyte peak occurred at the height of the empyema and was accompanied by an increase in the percentage of stab neutrophils; the blood picture from the 15th to the 18th day was that of a progressive "regenerative shift to the left" and would ordinarily be interpreted as indicating a grave prognosis. If conclusions may be drawn from this small series of cases, the presence of immature myeloid elements in the peripheral blood in lobar pneumonia apparently has, at best, a very limited prognostic significance. One patient who died (F. M., Chart I) exhibited a definite "regenerative shift" on the 7th day, but the myelocyte increase occurred at about the same stage of the disease, in relation to the initial infection, as in recovered patients.

Small numbers of myelocytes in the circulating blood during the febrile period of the infectious diseases are not unusual; they have been observed in sepsis and in many infections (Schindler,³ Schilling,⁵ Naegeli⁹ and others). In these cases myelocytes usually appear in the peripheral blood at a time when there is a marked increase in neutrophilic stab forms and is interpreted as being due to excessive stimulation of the bone marrow, resulting in the premature delivery of cells before they have reached the stab stage in their development. In lobar pneumonia, however, the maximum myelocyte response occurs at a time when the acute manifestations of the disease are subsiding; the temperature is normal or has approached normal and the commonly accepted evidences of bone marrow activity (total leukocyte count and, in particular, the percentage of stab

forms) are diminishing. Clinically, the myelocyte peak is accompanied by signs of resolution of the consolidated lung. Both clinical and hematologic conditions are quite different from those which prevail during the usually mild myelocytosis occurring during the acute stage of lobar pneumonia and other infections.

The stimulus responsible for the appearance of up to 15 or 20% of cells not normally present in the peripheral blood is not apparent. A postfebrile myelocytosis is not common to the infectious diseases; it has not been observed in bronchopneumonia or influenza, or in the postfebrile period of artificial hyperthermia. It may be significant that the maximum number of myelocytes was found in the peripheral blood at the time of resolution of pneumonic tissue. During this period nuclear material is liberated from the resolving exudate in considerable amount; the stimulating effect of certain nuclear derivatives on the bone marrow is well known. Although there is no direct evidence to support such an assumption, it is possible that the stimulating effect of nuclear material liberated at the time of resolution may be responsible for the observed myelocytosis, which apparently occurs to some degree in the majority of patients recovering from lobar pneumonia.

Summary. 1. In 43 unselected cases of lobar pneumonia, the white blood cell response was studied in detail, using both fixed and supravital stained preparations.

2. In the majority of patients, small numbers of myelocytes were frequently found in the peripheral blood during the acute febrile period of the disease.

3. In patients who recovered, a consistent, and frequently striking, shower of myelocytes was observed in the peripheral blood during the period immediately following crisis and lysis.

4. It is suggested that the postfebrile myelocyte shower may be due to the stimulating effect of nuclear material liberated during resolution of the pneumonic exudate.

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EVANESCENT EFFECT OF INTRATIBIAL INJECTIONS OF BACILLUS WELCHII TOXIN IN RABBITS.*

BY LEONARD J. GOLDWATER, M.D.,

CLINICAL ASSISTANT VISITING PHYSICIAN, THIRD (N. Y. U.) MEDICAL DIVISION, BELLEVUE
HOSPITAL; INSTRUCTOR IN MEDICINE, UNIVERSITY AND BELLEVUE HOSPITAL
MEDICAL COLLEGE, NEW YORK UNIVERSITY,

JOSEPH E. CONNERY, M.D.,

ASSOCIATE PROFESSOR OF CLINICAL PATHOLOGY, NEW YORK UNIVERSITY; VISITING
PHYSICIAN TO BELLEVUE HOSPITAL,

AND

HARRY HEIMANN, M.D.,

NEW YORK, N. Y.

(From the Department of Medicine, University and Bellevue Hospital Medical
College, New York University.)

IN 1929 Torrey and Kahn,¹ by intratibial injection of 0.5 cc. of hemolysin free *B. welchii* toxin, produced in rabbits an anemia resembling, hematologically, pernicious anemia in man. Beard, Clark and Moses² confirmed the findings of Torrey and Kahn. Furthermore, these observers were able to relieve the anemia by the administration of suitable doses of a known potent extract of liver.

The purposes of our study were (a) to attempt to confirm the results of the above investigators, and (b) to apply their technique to the biologic assay of the potency of certain specific anti-anemic substances.

Materials and Methods. The animals used in the study were healthy adult rabbits of approximately the same age and weight. They were housed in individual cages and fed what was considered an adequate diet. The toxin was an hemolysin-free *B. welchii* toxin.† Blood was obtained from the marginal ear vein for numerical estimations, morphologic studies and reticulocyte percentage determinations. Hemoglobin estimations were made by the Klett-Newcomer method. Estimations were made at intervals short enough to permit detection of significant changes. The hematologic determinations were made by the same person throughout the period of study.

After a control period of 12 days 3 rabbits received a single injection of 0.5 cc. and 2 rabbits were given 0.75 cc. of toxin, respectively. The toxin was injected intratibially according to the technique of Kahn and Torrey.¹ Two additional rabbits were followed

* This is No. 1 of a series of studies on the assay of biologic materials used in the treatment of the macrocytic hyperchromic anemias.

† This toxin was supplied by Drs. Kahn and Torrey of the Cornell Medical College.

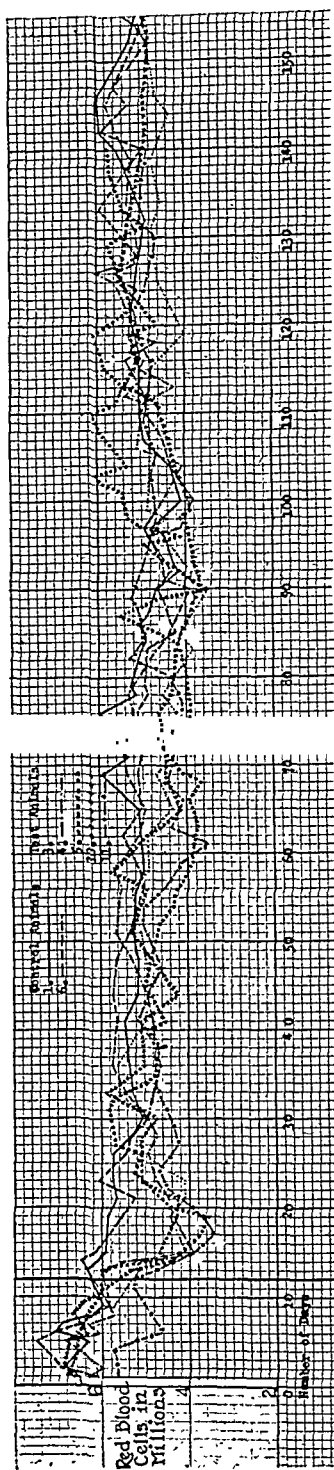


CHART I.—Total red blood cell counts in the rabbits. The heavy vertical line on the 12th day indicates the day of toxin injection.

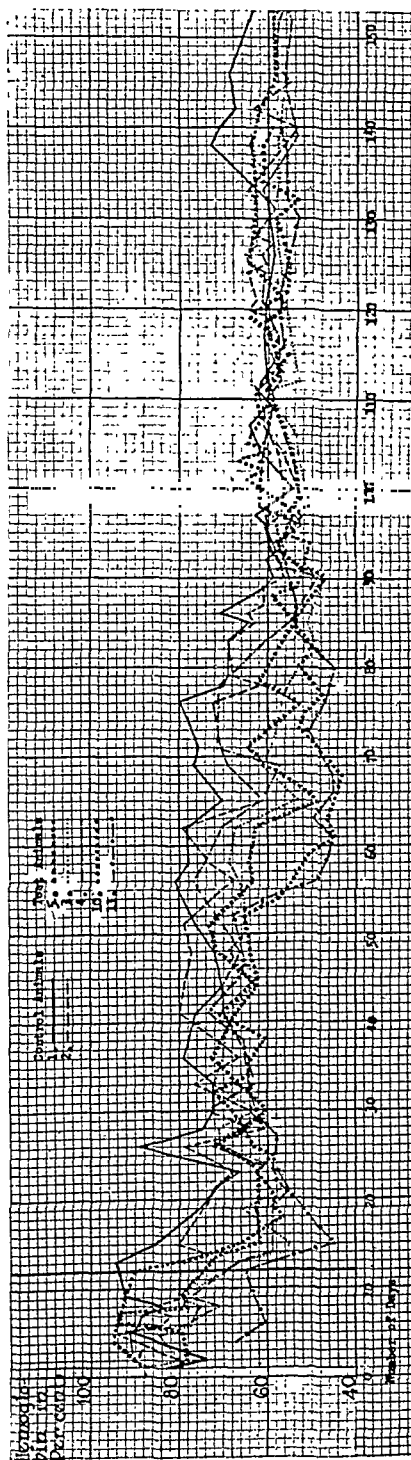


CHART II.—Hemoglobin determinations in the rabbits. The heavy vertical line on the 12th day indicates the day of toxin injection.

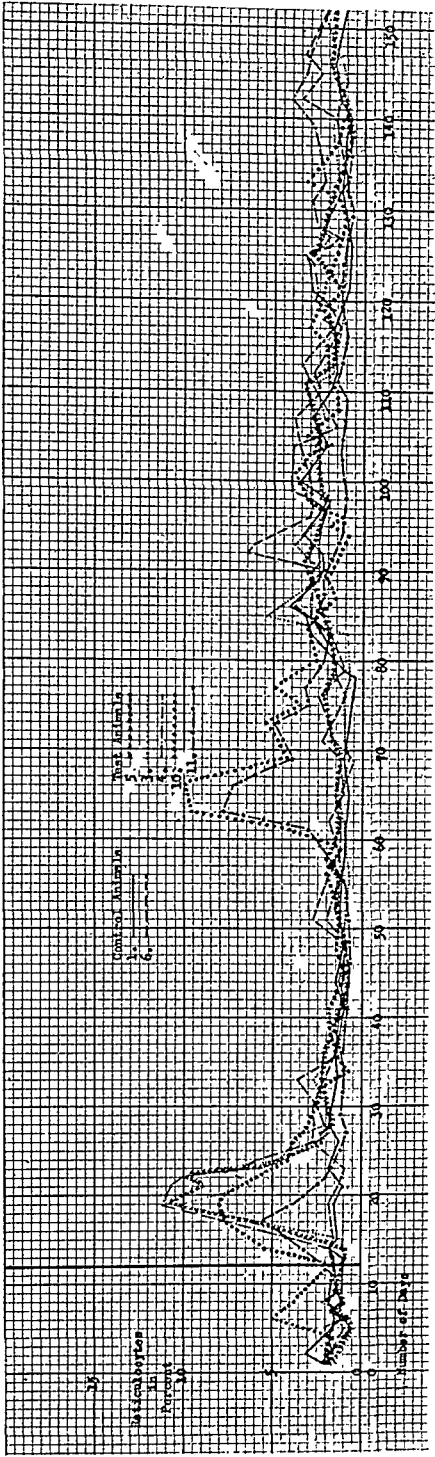


CHART III.—Reticulocyte percentages in the rabbits. The heavy vertical line on the 12th day indicates day of toxin injection.

as controls. The 7 rabbits were studied for 154 to 156 days. Since all the animals receiving toxin responded in practically the same manner regardless of the dosage of toxin, they were considered as a single group.

Results. *Red Blood Cells and Hemoglobin.* The red cells of the test animals showed a beginning fall on the day following injection of toxin (Chart I). The fall was maximal between the 5th and 7th days. No such fall was observed in the control animals. Following the initial fall there began a slow, steady rise of the curves, so that by the 110th day the curves of the test and control animals were at approximately the same level, and continued so thereafter.

The hemoglobin determinations (Chart II) closely followed those of the red blood cells.

Reticulocytes (Chart III). The reticulocyte curves rose as the total red blood cell counts fell; and again fell as the red blood cell counts rose. In the case of the 2 animals which were given 0.75 cc. of the toxin (Rabbits 10 and 11), rises were noted in the reticulocyte curves between the 60th and 70th days. The explanation for this finding is obscure. Interesting to note is the fact that a fall in the hemoglobin curves, also unexplained, occurred synchronously with the reticulocyte rises in the same 2 animals.

White Blood Cells. No significant changes in the curves of the white blood cells of the test or control animals were noted.

Morphologic Alterations in the Red Blood Cells. At no time during the experiment did the red blood cells of the test animals present the qualitative changes usually associated with pernicious anemia in man.

Color Index. The color index never rose to unity or above.

Summary and Conclusions. In our search to find a suitable method for assaying the potency of substances effective in the treatment of the macrocytic hyperchromic anemias we attempted to induce an anemia in rabbits by a single intratibial injection of hemolysin-free B. welchii toxin. Since the changes in the blood of the test animals were quite evanescent and since the blood picture of the test animals rapidly returned to a condition similar to that seen in the control animals, this method was deemed unsatisfactory for our purposes.*

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* From a personal communication from Dr. G. W. Clark we quote: "In a period from February 7, 1929, to March 4, 1931, 100 rabbits received intramarrow injections (tibia) using 37 different strains of B. welchii toxin prepared by the Anaërobic Department of the Lederle Laboratories and three welchii toxins prepared in one of the New York hospitals. None of these toxins has given the results reported earlier by Beard, Clark and Moses."

LACK OF EFFECT OF LIVER TREATMENT ON THE CIRCULATING RETICULOCYTES IN THE PIGEON.

BY HARRY HEIMANN, M.D.,

JOSEPH E. CONNERY, M.D.,

ASSOCIATE PROFESSOR OF CLINICAL PATHOLOGY, NEW YORK UNIVERSITY; VISITING
PHYSICIAN TO BELLEVUE HOSPITAL,

AND

LEONARD J. GOLDWATER, M.D.,

CLINICAL ASSISTANT VISITING PHYSICIAN, THIRD (N. Y. U.) MEDICAL DIVISION,
BELLEVUE HOSPITAL; INSTRUCTOR IN MEDICINE, UNIVERSITY AND BELLEVUE
HOSPITAL MEDICAL COLLEGE, NEW YORK UNIVERSITY,
NEW YORK, N. Y.

(From the Department of Medicine, University and Bellevue Hospital Medical
College, New York University.)

ACCORDING to Vaughan, Muller and Zetzel,¹ and Vaughan, Muller and Minot,² the feeding of an inadequate diet to pigeons results in a decrease in the percentage of the circulating reticulocytes. Further, the addition to the diets of materials effective in relieving the macrocytic hyperchromic anemias of man produces an increase of the percentage of the circulating reticulocytes of test animals. For these reasons, and because of the fact that the bone marrow of pigeons is megaloblastic, it seemed to Vaughan and her collaborators that pigeons might be used in the biologic assay of the potency of materials used in the treatment of anemia associated with a megaloblastic type of bone marrow (pernicious anemia).

The purposes of this study were (a) to test the validity of the above hypotheses and (b) to apply this technique to the biologic assay of the potency of materials used in the treatment of the macrocytic hyperchromic anemias.

Materials and Methods. Healthy adult pigeons were obtained from the open market and were housed in individual cages in a well ventilated room. Food and water were supplied in abundance and were changed daily. The cages were cleaned frequently without changing their relative positions in the room. Two diets were used: "complete" and "incomplete." The "complete" diet consisted of equal parts of flint corn, vetch, and Canada peas, and canary seed with abundant amounts of grit and lettuce. The "incomplete" diet consisted of the above without the canary seed, grit and lettuce. Three known potent commercial preparations of liver "fraction G" were used: (a) powdered extract, prepared from mammalian liver for oral administration,* (b) a solution of the same powdered extract for parenteral administration,* and (c) an aqueous solution pre-

* The mammalian liver fractions were supplied by the Lederle Laboratories.

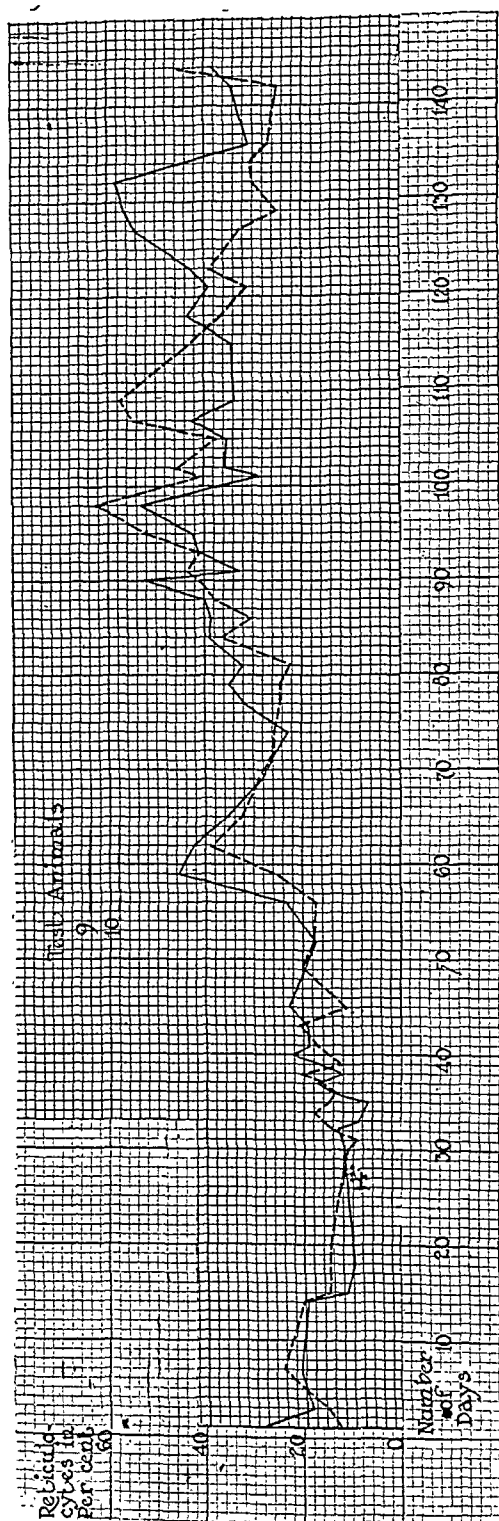


CHART I.—Reticulocyte percentages of pigeons on complete diet.

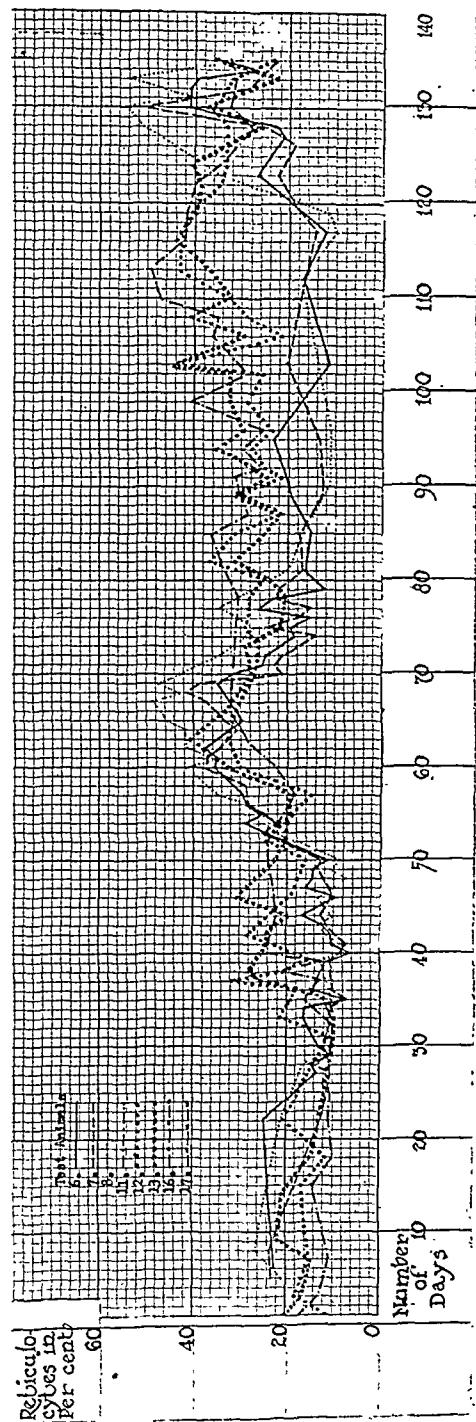


CHART II.—Reticulocyte percentages of pigeons on incomplete diet.

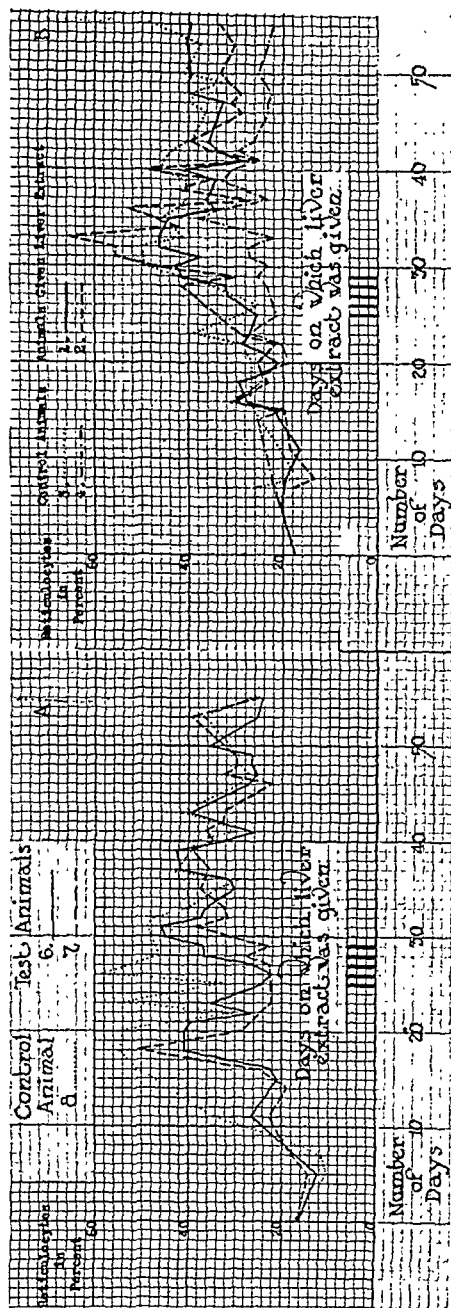


CHART III.—Reticulocyte percentages in pigeons which were given mammalian liver extract by mouth for five successive days. A, pigeons on "complete" diet; B, pigeons on "incomplete" diet.

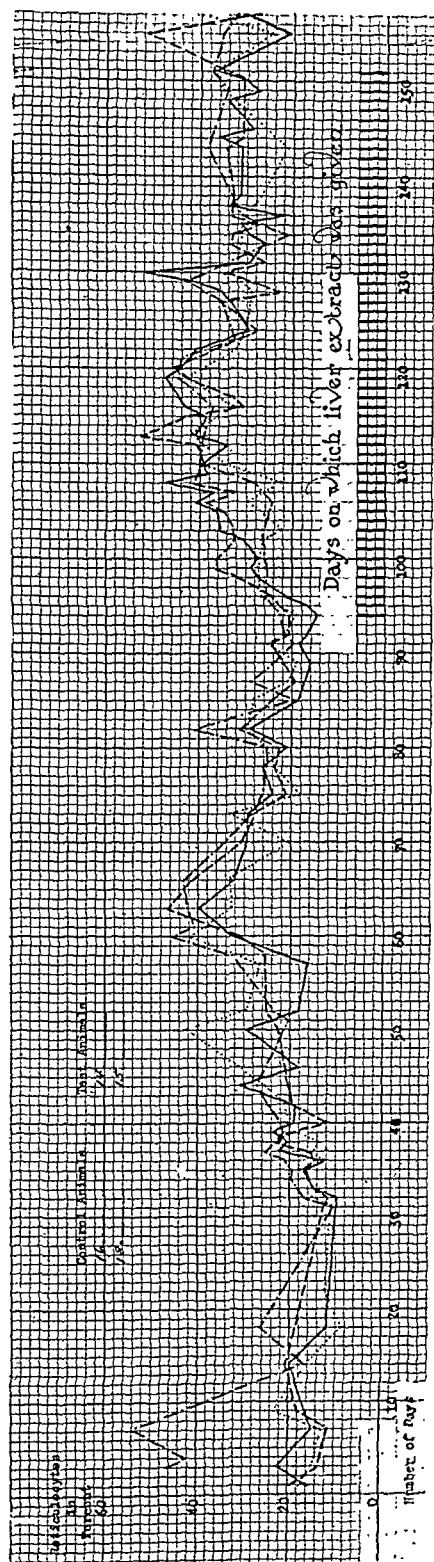


CHART IV.—Reticulocyte percentages in pigeons on the incomplete diet which were given mammalian liver extract by mouth for 57 successive days.

pared from the liver of the cod.* The powdered extract was used in solution of such concentration that 2 cc. contained the material derived from 4 gm. of raw liver. The powdered extract was given by stomach tube as was the fish liver extract. The solution for parenteral administration was of such strength that 5 cc. contained the material derived from 100 gm. of raw liver. All liver extracts were administered at the same time of day.

Blood for all examinations was obtained from the wing veins of the pigeons. Bleeding was easily controlled. Reticulocytes were counted according to Vaughan's modification¹ of Cunningham's method.³ All the red blood cells showing any reticulum in the cytoplasm were included as reticulocytes.† Hemoglobin estimations were made by the Klett-Newcomer method. Hematologic determinations were made frequently on samples of blood drawn at the same hour of each day. The birds were weighed about 3 times each week.

Results and Discussion. *Reticulocytes in Pigeons Receiving the "Complete" Diet.* Two pigeons were kept on the "complete" diet for a total of 144 days. As may be seen from inspection of Chart I, the reticulocytes showed considerable variations from week to week and even from day to day. The variations between two successive counts were often as great as 20% of the total red blood cells.

Reticulocytes in Pigeons Receiving the "Incomplete" Diet. Eight birds were kept on the "incomplete" diet for 135 days. From inspection of Chart II it can be seen that there is a downward trend of the circulating reticulocytes ending on about the 26th day, then an upward trend to the 65th day, followed by a second fall reaching its lowest level on the 74th day. Because of the undulatory character of the curves no prediction could be made as to the expected curve in any one case. By comparison of Charts I and II it can be seen that the individual variations of the reticulocyte percentages of the birds on both diets, "complete" and "incomplete," showed striking similarity.

Reticulocytes in Pigeons Receiving Liver Extract. From inspection of Chart III (A and B), it is apparent that the daily oral administration of potent liver extract (the material derived from 4 gm. of raw liver) for a period of 5 days produced no significant changes (a) in the type of the curves or (b) in the trends. This observation applies to pigeons receiving the "complete" as well as those receiving the "incomplete" diet. Because of the possibility that the test period of 5 days was not sufficiently long to permit of significant changes to occur, 2 birds which had been receiving the "incomplete"

* The fish liver extract was supplied by the White Laboratories.

† Some of the reticulocytes seemed to warrant separate enumeration because (1) of the density and amount of reticular material, (2) the fact that the reticulum encircled the nucleus, completely in many cases, and (3) the ease with which these cells could be identified. Irrespective of the dietary the number of these forms varied between 1% and 7% of the total red blood cells.

diet were fed potent mammalian liver extract (the material derived from 4 gm. of raw liver) daily for a period of 57 days (Chart IV). Here, again, it may be observed that the feeding of potent liver extract in large daily doses over a long period of time was without effect on the circulating reticulocytes in the blood of the test animals. In order to obviate the possibility of the failure of absorption of anti-anemic substances from the gastro-intestinal tract of the test birds⁴ being responsible for the lack of effect on the circulating reticulocytes, 2 pigeons receiving the "incomplete" diet were each given 1 cc. (containing the material derived from 20 gm. of raw liver) of a solution of liver extract by injection into the breast muscles. This experiment yielded negative results. As a further observation, 2 pigeons, also receiving the "incomplete" diet, were fed large daily doses of potent fish liver extract for 15 days, also without effect on the circulating reticulocytes.

Conclusions. From these experiments the following conclusions seem warranted:

1. The percentage of the circulating reticulocytes in the blood of the pigeon is subject to wide fluctuations.

2. The various test substances used in this study, including the "incomplete" diet, had no significant effect upon the percentage of the circulating reticulocytes in the pigeon.

3. In our hands this technique does not lend itself to the biologic assay of the potency of materials used in the macrocytic hyperchromic anemias.

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SPONTANEOUS RUPTURE OF THE HEART SIMULATING SURGICAL ABDOMINAL DISEASE.*

BY HARRY A. SALZMANN,

ASSISTANT, SURGICAL SERVICE, NO. 2, MT. SINAI HOSPITAL; ASSISTANT, SURGICAL
SERVICE OF DR. P. A. MC CARTHY, PHILADELPHIA GENERAL HOSPITAL,
PHILADELPHIA, PA.

(From the Staetische Krankenanstalten, pathological institute, Professor Loeschke,
director, Mannheim, Germany.)

FOLLOWING infarction of the myocardium, the patient may die, healing by scar formation may take place, or less frequently spontaneous rupture of the heart may result. That such grave changes

* Read before the Southeastern Branch of the Philadelphia County Medical Society, February 1, 1934.

in the heart muscle, even where rupture occurs, may assume the clinical picture of an abdominal catastrophe is not generally appreciated.

Four cases of spontaneous rupture of the heart and one of rupture of an aortic aneurysm, all admitted to the surgical division of the hospital because of suspected acute abdominal disease, have led us to consider this rather rare condition more closely. The fact that abdominal pain not infrequently is the only important symptom in disease of the cardiovascular system and may lead to confusion with lesions requiring operative treatment makes this condition of particular interest to the clinician.

In 5000 postmortem protocols, I was able to find only 6 cases of proven spontaneous cardiac rupture and 1 of rupture of an aneurysm of the aorta causing tamponade of the heart.

One may realize the rareness of this condition from the following: Krumbhaar and Crowell found only 7 cases in 16,000 autopsy reports; Romeick (Munich) 7 in 13,000 protocols, and in 8000 autopsies at Leipzig only 9 cases of spontaneous rupture of the heart were found.

A report of our own cases with a brief abstract of the clinical and post-mortem findings follows:

CASE 1.—W. W. (946/1931), aged 51 years, male, carpenter, had vague abdominal pains for the past 3 or 4 years; and recently, attacks of weakness and dizziness. Five days before admission he was suddenly seized with severe pains in the upper abdomen, vomited and was treated for suspected gall-bladder disease. He then attempted to get up out of bed but suddenly collapsed and was immediately brought into the hospital in a condition of shock.

Physical examination revealed an emaciated male, pulseless, and complaining of excruciating pains in the upper abdomen. The mucous membranes were pale; the respiratory excursions were rapid and shallow. The cardiac border was somewhat enlarged to the left, heart tones were weak and the heart action was irregular and rapid, no murmurs nor pericardial friction rub were heard; the radial pulse could not be felt; the patient vomited continuously. The abdomen was not distended, there was circumscribed tenderness on pressure in the epigastrium; the abdomen was otherwise negative except for slightly increased tension in the epigastrium.

The first thought was that we were dealing with a covered perforated ulcer. Because of the poor general condition of the patient operation was delayed. Following supportive treatment the pulse improved after several hours. Fluoroscopic examination of the abdomen gave a negative result. The Roentgen ray shadow of the heart showed a marked enlargement and a mitral configuration. Thirteen days after the onset of the present illness the patient had an anginoid attack, he again became pulseless and the temperature rose to 103.1°; at this time he again complained of severe pains in the upper abdomen. Two days after this attack the patient's condition became somewhat better and he was transferred to the medical division with the diagnosis of coronary sclerosis and thrombosis.

A Roentgen ray taken 16 days after the onset of the present illness gave the following findings: indefinite cardiac silhouette with considerable widening toward the left, and with some widening toward the right. The configuration of the cardiac outline is flabby. Pulsation could be seen only in the region of the large vessels. The cardiac border pulsated very un-

equally. The cardiac diameter was 17.6 cm. Electrocardiograph diagnosis on the same date: perpetual arrhythmia and tachycardia, severe heart muscle damage. Cardiac infarct?

The patient suffered several aginoid attacks and finally he became comatose; the coma was attributed to uremia. U.N. was 225. His coma became more pronounced until he died 27 days after the onset of the present illness.

Autopsy (167/1931): Sclerotic closure of the posterior coronary artery. Cardiac muscle infarct with perforation on the posterior wall of the left ventricle and large hemorrhage into the pericardial sac. Anemic infarcts of the kidneys. Radiating scar of ulcer in the fundus of the stomach.

CASE 2.—The patient was admitted to the surgical service with a history of severe kidney colic of several days' duration. He expired during the night of the same day.

Autopsy: Coronary sclerotic areas of myomalacia on the posterior wall of the left ventricle with perforation of the myocardium. Hemopericardium. Incomplete thrombosis of several of the arteries of the right kidney. Chronic pyelitis of the right kidney.

CASE 3.—The patient was admitted to the hospital for colicky pains suggestive of gall stones of 8 days' duration. He expired 15 minutes later.

Clinical diagnosis: Pancreatitis?

Autopsy: Atheromatous, and partially stenosing sclerosis of the coronary vessels. Perforation of the anterior wall of the left ventricle at the site of infarction, cardiac tamponade.

Lisa and Ring have recently reported an interesting case of occlusion of both coronary arteries with infarction and perforation of the left auricle. The patient was a 53-year-old white male, who gave a history of recurrent attacks of severe epigastric pain relieved by vomiting and alkalis. The symptoms lasted over a period of 4 years and the patient was subjected to operation on two different occasions. At first an appendectomy was performed and an apparently normal appendix was removed, with no relief of symptoms. A year later a diagnosis of duodenal ulcer was made and the patient was at first treated by Sippy diet with no relief. An electrocardiogram showed abnormal inversion of the *T* wave in Leads I and II and a suggestion of a coronary *T* wave in Lead III. In spite of the evidence of coronary lesions the patient's abdominal symptoms became so severe that a gastroenterostomy was performed, although no ulcer was found at operation. After a stormy convalescence he left the hospital. The symptoms became more severe and a year before his final illness he began to have precordial pain and showed clinical signs of decompensation such as cyanosis, edema, pleural effusion, and gallop rhythm. The patient finally died 4 years after the onset of symptoms and autopsy revealed occlusion and sclerosis of both coronaries with infarction and perforation of the left auricle just above the base of the posterior mitral cusp.

CASE 4.—J. B. (3337/1926), a 50-year-old laborer, claims that he was never seriously ill until present illness. On the day of admission he was seized with excruciating pains in the upper abdomen and was sent into the hospital for operation with a diagnosis of cholelithiasis or pancreatitis.

Physical examination revealed a well-developed male; with irregular heart action, and small, rapid pulse. The abdomen was slightly distended

and diffusely tender, especially in the upper abdomen to the right of the mid-line. After the administration of cardiac stimulants immediate operation was undertaken. Upon opening the abdomen the gall bladder appeared macroscopically diseased and was removed. During the operation cardiac stimulants had to be administered repeatedly; near the end of the operation the patient improved. The wound healed *per primam* and the patient felt very well. Histologic examination of the gall bladder revealed no inflammatory changes. On the 12th day following operation while the patient's condition was very good he suddenly developed air hunger, became very weak and expired almost immediately.

Clinical diagnosis: Cholecystitis; postoperative pulmonary embolism.

Autopsy: Luetic aortitis with two aneurysms; rupture of the intrapericardial aneurysm situated in the beginning portion of the aorta with hemo-pericardium and cardiac tamponade.

CASE 5.—The patient had severe upper abdominal pains of 2 days' duration; sudden death 2 days following admission.

Autopsy: Cardiac rupture in the middle of a myomalacious focus of the anterior wall of the left ventricle. Obliteration of the left coronary artery. Dilatation of both ventricles. Advanced generalized arteriosclerosis.

CASES 6 and 7, developed cardiac rupture unaccompanied by abdominal symptoms.

CASE 6, *Autopsy:* Perforated cardiac aneurysm. Coronary sclerosis.

CASE 7.—A. L., 59-year-old male, was brought into the hospital dead after having suddenly collapsed and it was supposed that death was due to an apoplectic stroke.

Autopsy: Perforation of the left ventricle. Coronary sclerosis.

The following tables present a short review of our own cases and Krumbhaar and Crowell's cases.* Table 1 shows the cases arranged according to the underlying disease. As many of the series in the first column were from old reports they undoubtedly understate the frequency of infarct formation (see high incidence of "fatty heart").

TABLE 1.—ETIOLOGY.

	Krumbhaar and Crowell series.	Author's series.	Total.	Per cent.
Coronary sclerosis with occlusion and infarct formation . . .	145	93	238	32.9
Coronary disease combined with various myocardial lesions . .	113	5	118	16.3
Cause undetermined; coronary arteries apparently normal . .	11	...	11	1.6
Coronary arteries not described .	68	4	72	10.0
Heart apparently normal . . .	5	...	5	0.7
Fatty heart	186	1	187	25.9
Myomalacia	42	1	43	6.0
Aneurysms	32	2	34	4.5
Malignant endocarditis	1	1	0.1
Lues	5	1	6	0.8
Tuberculosis	1	...	1	0.1
Abscess following septicemia	6	6	0.8
Echinococcus cyst	2	...	2	0.2
Tumor metastases	1	...	1	0.1
Total	611	114	725	100.0

* Davenport, A. B. (AM. J. MED. SCI., 176, 62, 1928) reports 57 cases gathered from the literature, but since the author's references were not published, we are unable to include his material in this analysis.

Table 2 gives a summary of the position of the perforation. According to this the left ventricle is most frequently the site of rupture.

TABLE 2.—SITE OF THE RUPTURED AREA.

	Krumbhaar and Crowell series.	Author's series.	Total.	Per cent.
Right auricle	35	1	36	5.2
Left auricle	12	2	14	2.0
Right ventricle	63	10	73	10.5
Left ventricle	493	61	554	80.0
Mixed	15	1	16	2.3
Total	618	75	693	100.0

The area of predilection for the perforations in the left ventricle is the apical region, where the infarcts and the conditions arising from them are chiefly located and where, as Meyer states, the muscle layer of the heart wall is physiologically thinnest and also where, as Boettger claims, the pressure which the left ventricle has to withstand is supposed to be most forceful. Next in frequency to the apical region is the posterior wall of the left ventricle. The average age of the patients in whom we find a perforation of the auricle is less than in cases of ventricular perforation.

The actual mechanism of tear and rupture has never been fully explained. The chief factors at work in the infarct are softening, hemorrhage and the action of the adjacent active muscle surrounding the infarct. The internal opening of the perforation is usually placed at the base of a papillary muscle or at the junction of the septum and the outer heart wall; both points which are subjected to the stress of divergent action of the two main muscle masses. The presence of excessive mural fat, as was found in all of the cases reported by us, is responsible for the rapidity with which necrosis and the formation of a perforation takes place.

Table 3 gives a review of the age of the patients.

TABLE 3.—INCIDENCE ACCORDING TO AGE.

	Krumbhaar and Crowell series.	Author's series.	Total.	Per cent.
Over 85	30	3	33	4.7
80+	52	11	63	9.0
70-80	167	42	209	30.0
60-70	188	21	209	30.0
50-60	81	16	97	13.9
40-50	43	1	44	6.3
30-40	23	..	23	3.3
20-30	6	1	7	1.0
10-20	8	..	8	1.2
1-10	4	..	4	0.6
Total	602	95	697	100.0

The incidence of rupture in cardiac infarction has been estimated by Benson and Hunter and by others (*vide* Beresford and Earl) as about 6%. This is confirmed in the present review.

Among the 5000 autopsy protocols examined we were able to find a pathologic condition of the circulatory organs in 1224 cases in which the heart was affected 1142 times. Coronary sclerosis was found in 658 cases, 75 of which had progressed to occlusion with concomitant infarction; an indisputable spontaneous rupture of the heart could be shown only in 6 cases (8%). Of these, 5 were due to coronary sclerosis with occlusion and infarct formation; 1 to an aneurysm of the left ventricle.

Although the diagnosis of cardiac perforation was not made in any of the cases, nevertheless, only 1 of our 5 cases with abdominal symptoms was operated upon. The clinical phenomena in all of the cases were so severe that the patients had been sent in for immediate operation. However, it was deferred because the severity of the spontaneous abdominal pains was incompatible with the very moderate rigidity of the abdominal wall. The fact that the pain radiates upward under the sternum and possibly to the shoulder, especially toward the left shoulder and also the fact that tenderness to palpation in the upper abdomen is only moderate or absent, together with the history of previous attacks attributable to arteriosclerosis and/or myocardial changes (fainting spells, angina pectoris, dizziness, anxiety, etc.) all serve as points in the determination of the diagnosis.

In view of the etiology and the progressive myocardial damage we must regard surgical therapy as seemingly hopeless. The formation of connective tissue in cardiac muscle wounds is very light. For this reason the danger of a secondary hemorrhage due to a rupture of an insufficiently developed scar and the possibility of aneurysm formation is great, as has been pointed out by Klose.

The fact that myocardial infarction, even when severe enough to end in perforation of the heart, and even to a greater degree perforation of the aorta, and dissecting aneurysm of the aorta, may give rise to a symptom complex which may easily be confused with that of a pancreatic necrosis, cholelithiasis or nephrolithiasis is not sufficiently recognized. These conditions of the circulatory mechanism may lead to severe abdominal pain, frequently accompanied by vomiting and distention. If one finds these signs in older individuals and at the same time signs of severe myocardial degeneration are present (such as arrhythmias), one should always consider in such cases whether the pains are not the result of a cardiac condition. The question as to whether they are to be regarded as angina abdominalis caused by arteriosclerotic changes of the abdominal vessels, as described by Ortner, or whether they are to be regarded as cardiogastric pains due to distention of the pericardial sac, still remains open.

Levine, in his monograph on infarction, found that of 9 patients in whom rupture had occurred, 8 died within 2 weeks following the onset of infarction; of these 6 died between the 5th and 14th day. This, according to Levine, is the period when necrosis is most marked and the muscle is softest. The difficulty of differentiating between the symptoms of infarction and those of rupture make it impossible to calculate the length of survival after rupture has taken place.

A critical review of the cases reported in the literature as having lived for days or even weeks after rupture has occurred leads one to the conclusion that the symptoms of infarction have been confused with those of perforation. The mechanism of death in spontaneous rupture may theoretically be explained as based on the obstruction of the great veins by the raised intrapericardial pressure. In those cases where little blood is found in the pericardial sac the sudden death suggests ventricular fibrillation or some such disaster.

Summary. 1. Six cases of spontaneous rupture of the heart and 1 case of perforation of an aortic aneurysm are reported; 718 cases of spontaneous cardiac rupture gathered from the literature are reviewed.

2. Cardiac rupture most frequently occurs in an area of infarction 5 to 14 days following coronary occlusion. The most common site of the rupture is the left ventricle.

3. An important item for the clinician is that of differential diagnosis, because the condition frequently arises with severe symptoms attributable to diseased conditions of the abdominal organs. It may lead to confusion with pancreatitis, gall bladder and kidney colic, intestinal ileus, and other diseases of the abdominal viscera.

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ENLARGEMENT OF THE HEART DUE TO ABNORMAL GLYCOGEN STORAGE.

IN VON GIERKE'S DISEASE.*

BY WILLIAM ANTÖPOL, M.D.,

JULIUS HEILBRUNN, M.D.,

AND

LESTER TUCHMAN, M.D.,

NEW YORK CITY, N. Y.

(From the Pediatric Service and the Laboratories of Christ Hospital, Jersey City, N. J., and the Laboratories of The Mount Sinai Hospital.)

GLYCOGENOSIS, or glycogen storage disease, was first described by von Gierke,¹ in 1929, as a pathologic entity under the name of "hepato-nephromegalia glycogenica." He gave a detailed pathologic description of 2 cases with massive glycogen deposits in the liver and kidneys. Schoenheimer² confirmed von Gierke's histologic findings by chemical analyses and attributed the disorder to a disturbance of the glycogen splitting mechanism.

Five necropsy reports of this disease are now on record, in 2 of which tremendous diffuse enlargement of the heart is described (Putschar³ and Pompe⁴).

The present communication deals with a case which was clinically

* Presented before The New York Pathological Society, October 26, 1933.

obscure, and which terminated with an intercurrent pneumonia. The markedly enlarged heart found at necropsy gave rise to the suspicion that the case was one of glycogenosis. Histopathologic and chemical studies proved the correctness of this opinion.

Case Abstracts.—R. K., a 4½-month white, German, male, was admitted to the Christ Hospital, Jersey City, N. J., on the service of Dr. Julius Heilbrunn on August 17, 1933. The mother had borne another child, now living and apparently normal. Two weeks prior to the birth of the patient, the mother showed a trace of sugar in the urine. From birth on the breathing of the infant was unusually rapid.

The weight at birth was 3250 gm.; 10 days later 3559 gm. The average weekly gain was 110 gm. except for the 4 weeks prior to admission, during which the child failed to gain.

Physical Examination. The general appearance is that of a fairly well-nourished infant, who does not appear acutely ill. The only positive findings are slightly enlarged cervical glands. Forty-eight hours after admission bronchial breathing and dullness over the right lower and middle lobes appear. The respirations are rapid and shallow, the facial expression anxious, and the features pinched. A diagnosis of pneumonia is made. Four days later, the left side of the chest shows similar findings.

Laboratory Findings: Hemoglobin, 75% (Sahli); white blood cells, 7800; polymorphonuclears, 28%; lymphocytes, 72%. Routine examination of the urine was negative. No examination for acetone.

Roentgen ray of chest 4 days after admission shows cardiac enlargement with no definite indications of pulmonary disease.

Roentgen ray of chest 1 day before death shows marked enlargement of the heart to the right and left with scattered areas of consolidation in the right upper lobe and a slight pleural exudate. The cardiac shadow obscures the underlying details in the left lung.

The infant did poorly in the hospital. Profuse diaphoresis, restlessness and cyanosis were the most prominent symptoms. During the 10 days in the hospital the weight declined 112 gm. The temperature was slightly elevated until the 10th day when it rose to 108° just before death.

Necropsy. We are indebted to Dr. F. H. Hemsath, pathologist, for the use of this material. Only a partial examination was permitted.

Heart. The heart is strikingly enlarged and weighs 85 gm. The pericardial cavity contains no excess of fluid. The pericardial surfaces are smooth and glistening. The presenting anterior surface is made up of both right and left ventricles (Fig. 1). The heart is in a state of contraction. The right auricular wall is moderately thickened, the right ventricle markedly so (10 to 16 mm.); the interventricular septal portion is 18 to 25 mm. thick. The left auricle is moderately hypertrophied and the endocardium is white, but smooth throughout. There is marked hypertrophy of the left ventricle (10 to 18 mm. thick). The very large and prominent papillary muscles almost completely fill the cavity of the contracted chamber. No changes are noted in any of the valves. The aorta is negative. The isthmus of the aorta is not narrowed.

Microscopic Examinations. The myocardium is composed of a network of cytoplasm of varying thickness (2 to 4 microns) (Fig. 2-A). In those places where the muscle is cut tangentially, the muscle cells appear in the form of hollow cylinders surrounded by delicately striated protoplasmic walls (Fig. 2-B.) The nuclei of the interstitial cells are for the most part compressed. The muscle nuclei, about 8 microns in diameter, are peripherally situated, have a definite nuclear membrane, and a moderate amount of chromatin material. Occasional atrophic muscle fibers as well as focal fibrotic areas are seen throughout the myocardium. An occasional small

collection of neutrophils and round cells is present. Perivascular fibrosis is prominent. The subendocardial connective tissue is widened.

The shrinkage is not as marked in the celloidin embedded tissue and the walls of the hollow cylinders appear thicker. Best's carmin stain shows the intracellular non-protoplasmic areas to be filled with rods and droplets which stain a deep brilliant red (Fig. 3). Similar droplets are noted in the interstitial tissue. These rods and droplets stain brown with iodine. Comparison of serial sections with both of these methods does not reveal any appreciable difference in the amount of stained substance, thus ruling out the presence of significant quantities of galactogen.⁵

The Sudan stain reveals a slight amount of neutral fat in the interstitial tissue. No neutral fat is present in the muscle fibers.

BLOODVESSELS. Microscopic Examination. Many of the bloodvessels are thickened, because of swelling of the muscle fibers. The muscular layer of the vessels, especially the larger veins, appears as a thin network of cytoplasm, and resembles the network described in the heart except that no striations are visible. The endothelium is swollen, and the elastica is prominent. The muscle fibers of the aorta and pulmonary artery present a similar picture. There is, however, an increase in the connective-tissue framework between the muscle fibers.

Best's carmin stain demonstrates glycogen droplets, which fill the vacuoles in the individual muscle fibers. This is very striking in longitudinal sections where the fusiform glycogen accumulations are seen in parallel rows. The endothelium is also filled with glycogen. Glycogen droplets are present within the lumen of many of the vessels.

LIVER. The organ is enlarged. Its capsule is smooth. On cut section it has a grayish appearance. The lobular structure is not discernible.

Microscopic Examination. Hematoxylin-eosin stain reveals crowded cells with very few blood spaces between them (Fig. 4-A). The cell membrane is prominent. The cytoplasm of the liver cords contains both vacuoles and granules. The cells in the periportal areas are larger than the central cells, and are more frequently vacuolated. The nuclei are large, round, and eccentrically situated. Scattered throughout the parenchyma there are focal collections of neutrophils with an occasional round cell. Cellular structure is absent in these areas. The cells lining the smaller biliary channels are swollen and almost completely fill the lumen. There is no inflammatory exudate within, and only an occasional leukocyte about the bile channels. The Kupffer cells are not prominent.

Best's carmin stain shows fine red-staining droplets within the liver cells. The larger, and more vacuolated cells contain fewer of these. The cells of some of the bile channels, especially those of smaller order, show similar changes. Red-staining droplets are also found within the lumen of the larger biliary ducts. Glycogen is not present in any of the nuclei, and only a very occasional Kupffer cell contains this substance.

In portions of the section in which the fixation is not quite satisfactory, intercellular spaces, as well as intracellular bile canaliculi are seen outlined against the clear background. These portions resemble a preparation stained for bile capillaries.

The cells within the capsule of the liver contain glycogen.

The Sudan stain on frozen sections reveals neutral fat, chiefly in the cells of the periportal areas.

KIDNEY. Only portions of the kidney were obtained, and the weight could not be determined. The yellowish-gray cortex and the darker gray medulla are well delimited.

Microscopic Examination. Hematoxylin-eosin stain: Many of the glomeruli retain their fetal form. Some of the cells of the proximal convoluted tubules have a granular, others a clear cytoplasm. The lining

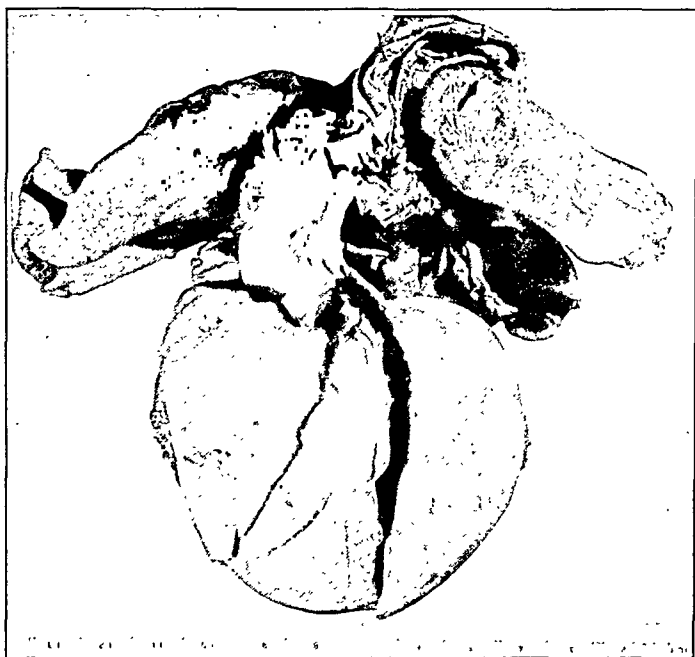


FIG. 1.—Anterior view. Both ventricles form the anterior surface of the heart. Lungs are left attached for comparison with the size of the heart.

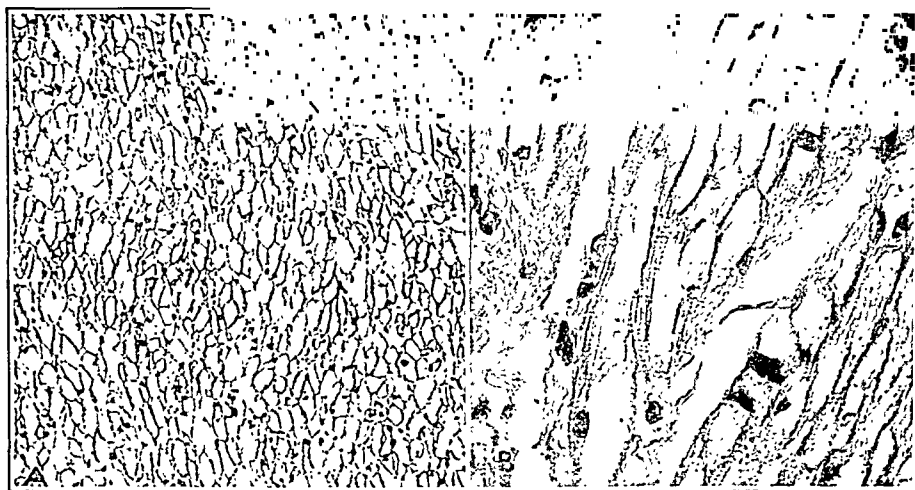


FIG. 2A.—Myocardium. Low-power view, showing the cytoplasmic network (hematoxylin-eosin stain).

FIG. 2B.—Myocardium. High-power view of an area in which the fibers are cut tangentially, showing hollow cylinders with striations in the muscular wall (iron-hematoxylin stain).



FIG. 3.—Myocardium. High-power stained with Best's carmin method. The gray rods and droplets correspond to the red staining glycogen.

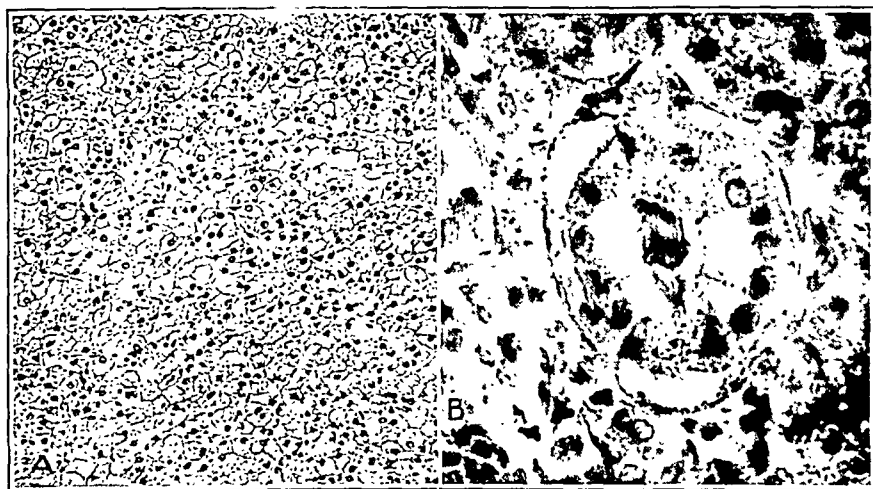


FIG. 4A.—Liver. Low-power view.

FIG. 4B.—Kidney. Best's carmin stain, showing droplets of glycogen within the cells and a mass of glycogen in the lumen of a collecting tubule.

cells are swollen, bulge into the lumen, and in many places completely occlude it. The cytoplasm of the cells of the proximal portion of the descending loop of Henle is similar in appearance, but not quite as abundant. The ascending loops are diffusely pink-staining. The cytoplasm of the distal convoluted tubules, the collecting and the uriniferous tubules is similar to that of the proximal convoluted tubules. The bloodvessels are thickened. Best's carmin stain reveals glycogen in many of the glomeruli, in Bowman's space, and also within the cells lining the capsule, also within the cells of the proximal convoluted tubules, the distal convoluted tubules, the collecting tubules, and the uriniferous tubules. Very little glycogen is present within the lumen of these structures until the collecting tubules are reached, where an appreciable amount is seen (Fig. 4-B).

LUNGS. There is an area of bronchopneumonia in the right upper lobe.

THYMUS. There is necrosis in the center of many of Hassall's corpuscles. Glycogen is present within many of the cells, especially the peripheral layers of the corpuscles.

CHEMICAL ANALYSIS OF ORGANS. The formalin fixed material was placed in absolute alcohol 4 weeks after the autopsy. Analyses of the heart, liver, kidney and lungs were done by Pflüger's method. In spite of the fact that the specimens had been in 10% formalin for so long a period, the following amounts of glycogen were found: Heart, 3.57%; liver, 3.25%; kidney, 4.34%; lung, 0.32%.

Of these organs the only one which normally contains glycogen in substantial amounts is the liver. The chemical findings corroborate the histologic demonstration of glycogen, so that we are undoubtedly dealing with a case of abnormal glycogen storage in the von Gierke's sense. The formalin fixation precluded investigation of the glycogen ferments.

Discussion. Von Gierke's disease, or glycogenosis, is a metabolic perversion characterized by abnormal deposition (or storage) of glycogen, analogous to the abnormal storage of kersin and other lipoids in those well-studied errors of fat metabolism, Gaucher's disease and Niemann-Pick's disease. Yet, the analogy must not be pressed too far, as the latter represent definite storage preponderantly in the reticuloendothelial system. In the present disease the reticuloendothelial system is singularly free, the parenchymatous elements being the ones chiefly involved. The mechanism responsible still remains to be elucidated.

A persistence of the fetal type of glycogen metabolism into post-natal life is probable. It is known that fetal glycogen does not disappear so rapidly by spontaneous glycogenolysis, and cannot be mobilized readily by cold or adrenalin.^{6, 8} In the fetus, glycogen deposits in the kidneys, bloodvessels, and organs of internal secretion are present, but in extrauterine life the occurrence of glycogen in these sites is strictly pathologic.

The biochemical etiology of this disease is still obscure. Against the assumption that the glycogen itself is chemically different or biologically inert, evidence is presented by Schoenheimer that glycogen isolated from a case of this disease had the usual physical

and chemical properties, and could be hydrolyzed by normal liver tissue. The complete absence of glycogenolytic enzyme in the diseased liver seems unlikely. On the other hand, increased amounts of amylase were observed in the urine of some of these cases. The amylase titer of the serum in this condition deserves further study; the glycogen content of the serum is occasionally reported as increased. Thus it seems that the glycogen storage is neither due to a qualitative variation of the glycogen, nor to a lack of glycogenase, but to an unexplained inability of the enzyme to act on its substrate. This may be due either to the presence of inhibitory substances, or to the absence of activators, or to the fact that the enzyme has no access of the substrate.

Deposits of glycogen may occur in the liver, kidneys, brain, heart, bloodvessels, muscles, and organs of internal secretion. The clinical picture depends upon the sites of deposition and upon the extent to which the vital processes of the affected tissues are interfered with. So far three main symptom groups are known, due to preponderance in liver and kidneys, in heart and bloodvessels, or in the brain. The first is the best known and possibly the largest group—the hepatonephromegalia glycogenica of von Gierke. The second group—that with cardiac hypertrophy—gives a clinical picture which, in the absence of proper chemical and histologic studies, may be confounded with the so-called idiopathic hypertrophy of the heart, as pointed out by Pompe.⁴

It is possible that many of the cases formerly classified as idiopathic hypertrophy belong to the von Gierke type of disease with enlarged heart, and that rhabdomyomata are localized collections of glycogen-rich fibers, possibly due to focal disturbance in glycogen metabolism. Virchow first recognized the relationship between so-called idiopathic hypertrophy and rhabdomyoma of the heart. As far back as 1900, Marchand¹⁰ and Askanazy¹¹ pointed out that rhabdomyomata of the heart were rich in glycogen. Schmincke¹² described the transition between isolated and diffuse rhabdomyoma of the heart and considered this a persistent embryonal state giving rise to hypertrophy. In many cases of the so-called idiopathic hypertrophy vacuoles have been noted in the heart muscle but were not explained and their association with large livers and enlarged kidneys is frequent. Sprague, Bland and White¹³ report enormous enlargement of the heart with vacuolization of the muscle fibers, as well as vacuolization of the hepatic cells. They do not explain these changes, typically those of glycogenosis, which apparently was not suspected.

The third group, *i. e.*, with cerebral symptoms due to glycogen deposits in the brain and spinal cord (Kimmelstiel¹⁴) makes necessary a review of all poorly understood cerebral conditions in children in order to determine whether some of them are not related to the effect of abnormal glycogen storage.

Summary. A case of von Gierke's disease with a markedly enlarged heart is presented. The possible relationship of this malady to idiopathic hypertrophy of the heart and diffuse rhabdomyoma of the heart is discussed.

After the presentation of this paper we were informed by Dr. K. Kato that he had observed 2 similar cases in Chicago.

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THE EFFECT OF ELEVATED METABOLISM ON THE HEART OF FRIZZLE FOWL. II. INCREASED RATIO OF HEART TO BODY WEIGHT.

BY ERNST P. BOAS, M.D.,
NEW YORK CITY,

AND

WALTER LANDAUER, PH.D.,
STORRS, CONN.

(From the Medical Service (Dr. George Baehr) Mt. Sinai Hospital, and the Storrs Agricultural Experiment Station.)

In a previous communication¹ it was pointed out that Frizzle fowl, a variety of chicken with scanty plumage, offer an opportunity of studying the effect on the heart of the increased basal metabolism, resulting from the profound disturbance in the conservation of body heat. It was shown that the heart rate of Frizzle hens is on the average 72 beats (27%), and of Frizzle roosters 117 beats (68%) above that of normal chickens. The conclusion was reached that the rapid heart rate of Frizzle fowl is conditioned by their elevated metabolism.

One of us (Landauer) had noted that the hearts of Frizzle fowl appear hypertrophied, elongated and relatively narrow. The following observations comprise a verification of this impression.

Method.—The study of heart weights is a difficult and painstaking procedure, and the results depend a good deal on the technique employed. In

our study an additional handicap lay in the fact that the birds were killed in Storrs, and their hearts weighed in New York City.

The determination of accurate heart weights involves the careful freeing of the heart of epicardial fat, bloodvessels and pericardium, and the establishment of a ratio between heart weight and body weight. This was first stressed by Müller.²

We followed the following procedure: The birds were weighed and immediately thereafter killed at Storrs. Then the heart was removed, and the gross weight of the undissected heart was recorded. The heart was then placed in 10% formaldehyde solution and was shipped to New York. Hermann³ has shown that a heart in 10% formaldehyde gains in weight during the first 2 to 4 days, and then gradually returns to the original autopsy weight in 6 to 10 days. For several days following there is very little change in weight. Thus, if a heart that has been placed in formalin is weighed between the 10th and 15th day after immersion into the solution, its weight will closely approximate the weight in the fresh state. Kirch⁴ made similar observations and demonstrated that the weights of the different chambers as well as their linear measurements change proportionately when the heart is fixed in formalin solution. As is shown in the tables, our chicken hearts were weighed and dissected at a time when their weights closely approximated their original fresh weights.

The actual procedure and dissection was carried out in the following manner. The heart was removed from the formalin solution and gently dried with a cloth. Any excess solution was gently expressed from the auricles. The whole heart was then weighed. A balance which was accurate to 0.1 gm. was employed for all of the weighing. In the chicken heart the fat is collected particularly in the auriculoventricular groove and at the roots of the aorta and pulmonary artery. This was carefully dissected away. The large vessels were left in place. Any excess fat in the epicardium was removed. The auricles were then separated from the ventricles by blunt dissection, leaving the upper surfaces of the ventricles perfectly smooth with intact musculature. An incision was then made down the posterior wall of the right ventricle along the septum. This incision is marked by a posterior descending branch of a coronary artery. Both the artery and the incision curve downward and reach the lower border of the right ventricle at a point about $\frac{2}{3}$ of the distance from the root of the aorta to the apex of the heart. The incision was then continued to the left and then upward along a line formed by the extreme limit of the cavity of the right ventricle and along the anterior border of the interventricular septum to and through the auriculoventricular ring. The root of the pulmonary artery and the aorta were then separated by blunt dissection along a line of natural cleavage. This cleavage was continued on the right ventricular aspect of the interventricular septum, and was marked by small deep septal branches of the coronary arteries,⁵ so that the musculature of the conus arteriosus was dissected free as part of the right ventricle. The pulmonary artery was then cut off just above the semilunar valves. The left ventricle was then opened by a cut along the posterior border of the septum paralleling the first cut of the right ventricle. The septum was then cut away along the line of attachment of the right ventricle. The aorta was cut off just above the semilunar valves.

The following weights were recorded: the undissected uncleaned heart, the cleaned heart, the auricles together, the right ventricle, the left ventricle, the interventricular septum.

Even in the hearts of humans and of large animals there has been great difficulty in establishing proper incisions that would lead to accurate separation of the cardiac chambers. The chief stumbling

block has been to determine how much of the interventricular septum belongs to the right, and how much to the left ventricle. Müller calculated that about 30% of the septum belongs to the right, and 70% to the left ventricle. Subsequent workers have criticized his technique and his calculations. Wideroe⁶ avoided the dilemma by ignoring the septum and using only those portions which were free of the septum. He thus established his ratio of right ventricle to left ventricle. Both Lewis⁷ and Hermann³ attempted to improve on these methods by carefully worked-out dissections. Such painstaking dissection, difficult enough in a large heart, is impossible to carry out with accuracy in the small hearts of chickens: so we adopted a rougher method, which more closely approximates the original one of Müller. We do not lay undue weight on our findings, therefore, insofar as the relative weights of the individual chambers are concerned, although results are sufficiently uniform to appear significant. The auricular weights are not always accurate, for not infrequently in removing the heart, part of the right auricle was cut off. We would lay particular emphasis on the combined weight of the two ventricles including the septum, for these are absolutely accurate.

It is well recognized that absolute heart weights have little significance, and that it is necessary for purposes of comparison to establish the ratio between heart weight and body weight. In the case of birds, it is advisable to deduct from the body weight the weight of the feathers, for the heart weight is proportional primarily to the weight of the skeletal musculature (Wideroe). Relying on the studies of Mitchell, Card, and Hamilton,⁸ we have arbitrarily estimated that in fully grown normal birds the plumage constitutes 8% of body weight in males, and 7% in females. For the Frizzle fowl we estimate the plumage as 5 grams, except for the lot of birds killed on October 16, 1933. For some reason these birds had a better developed plumage. For them we assumed a plumage weight of $\frac{1}{2}$ of that of normal chickens.

The hearts of 110 chickens were weighed. Of these 37 were normal females, 33 Frizzle females, 20 normal males, and 20 Frizzle males. The normal chickens were mostly Leghorns, with a few creepers and rumpless forms. The data, arranged according to body weight, appear in Table 1.* Table 2 presents the averages of the ratios: total cleaned heart weight times 1000, divided by body weight without feathers; total ventricular weight times 1000 divided by body weight without feathers; right ventricle divided by left ventricle including the septum; and right ventricle divided by the left ventricle, with the septum excluded. To the averages are appended the standard deviations from which the errors of the differences can be readily calculated.

* Because of lack of space the detailed protocols cannot be printed. The individual figures will be supplied by the authors on demand.

TABLE 1.—HEART WEIGHTS AND RATIOS.

Breed and sex.	Number of chickens.	Average body weight, grams.	Average body weight without feathers, grams.	Average heart weights.							Average ratios.			
				Uncleaned.		Cleaned, grams.	R V, grams.	L V, grams.	S, grams.	As, grams.	$\frac{H \times 1000}{B}$	$\frac{V \times 1000}{B}$	$\frac{LV + S}{RV}$	$\frac{RV}{LV + S}$
				Fresh, grams.	Fixed, grams.									
Normal females	8	1000	931	5.4	5.3	3.6	0.5	1.8	0.7	0.6	3.9	3.2	0.21	0.30
Normal females	9	1214	1127	6.1	6.0	3.9	0.6	2.0	0.7	0.7	3.4	2.9	0.22	0.30
Normal females	10	1400	1302	6.2	6.1	3.9	0.6	2.0	0.7	0.6	3.0	2.6	0.23	0.31
Normal females	10	1720	1600	8.0	7.8	4.8	0.7	2.4	0.8	0.8	2.9	2.5	0.22	0.30
Frizzle females	13	1239	1211	7.0	6.8	4.9	0.8	2.5	1.0	0.7	4.2	3.5	0.22	0.31
Frizzle females	10	1650	1603	8.3	8.2	5.8	0.9	2.8	1.2	0.9	3.6	3.1	0.24	0.34
Frizzle females	10	2036	2006	11.3	10.8	8.2	1.3	4.0	1.8	1.1	4.4	3.6	0.23	0.33
Normal males	10	1653	1521	8.2	8.2	6.6	1.0	3.6	1.0	0.9	4.3	3.7	0.23	0.30
Normal males	10	1924	1771	9.9	9.8	7.8	1.3	4.1	1.1	1.2	4.4	3.6	0.25	0.31
Frizzle males	10	2036	1963	13.5	13.3	10.5	1.4	5.6	1.8	1.6	5.3	4.5	0.20	0.27
Frizzle males	10	2562	2469	14.4	14.2	10.6	1.7	5.0	2.1	1.8	4.3	3.6	0.24	0.35

R V = right ventricle; L V = left ventricle; S = Septum; As = auricles; H = total cleaned heart weight; V = ventricular weight; B = body weight without feathers.

TABLE 2.—HEART RATIOS OF NORMAL AND FRIZZLE FOWL.

	No. of chickens.	$\frac{H \times 1000}{B}$		$\frac{V \times 1000}{B}$		$\frac{RV}{LV + S}$		$\frac{RV}{LV}$	
		Aver.	σ	Aver.	σ	Aver.	σ	Aver.	σ
Females: Normal	37	3.3	± 0.50	2.7	± 0.4	0.22	± 0.03	0.30	± 0.05
Frizzle	33	4.0	± 0.88	3.4	± 0.68	0.23	± 0.05	0.33	± 0.07
Males: Normal	20	4.2	± 0.36	3.6	± 0.28	0.24	± 0.03	0.31	± 0.05
Frizzle	20	4.8	± 1.3	4.0	± 1.1	0.22	± 0.06	0.31	± 0.13

H = heart weight; V = ventricular weight including septum; R V = right ventricle; L V = left ventricle; S = Septum; B = body weight minus feathers.

There are few available studies of the heart weights of chickens. Loer,⁹ employing Müller's method, weighed the hearts of 9 male and 13 female chickens aged 4 to 5 months. The ratio heart weight times 1000 to body weight was 4.1 for males and 3.8 for females. Wagner¹⁰ found that this ratio varied from 3.8 to 7.7. Ehrich and Cohn¹¹ report relative heart weights of 12 female Rhode Island Reds ranging in age from 1 to 8 years and find the heart-weight-body-weight ratio to be on the average 3. All of these figures correspond rather well to our total heart-weight ratios.

We wish to call attention particularly to the ratio of the total ventricular weight to the body weight, for this is the most accurate of our determinations. The difference between the averages of $\frac{V \times 1000}{B}$ of normal and Frizzle females is 0.7 with an error of ± 0.14 .

This difference is significant, so one may conclude that in proportion to body weight, the ventricles of Frizzle pullets are heavier

than those of normal pullets. The error of the difference of the male series is greater, so that taken alone, the figures would have no significance; but in view of the fact that they differ in the same direction as do the females, it seems safe to infer that the ventricles of Frizzle cockerels are heavier than those of normal cockerels. The variability of the whole heart ratios is greater, but they too behave in the same manner. The conclusion is justified that the hearts of Frizzle fowl, in relation to their body weights are heavier than those of normal fowl. The ratios between right and left ventricles, whether or not the septum be included, are practically the same for Frizzle and normal fowl. It seems, therefore, that both ventricles share equally in the hypertrophy that takes place.

A study of Table 1 reveals no significant difference between chickens under 1, and over 1 year of age in the ratio of ventricular weight to body weight. Nor is there a constant difference in this ratio if one compares smaller with larger chickens of the same sex and breed. It is strikingly evident that the heart-weight-body-weight ratio of Frizzles is much more variable than that of normal fowl. This is due undoubtedly, to variation in the amount of plumage, and in the reaction of the bird thereto.

The relative heart weights, whole heart to body weight as well as ventricular weight to body weight of males, both normal and Frizzle, are greater than those of females.

Our findings of cardiac hypertrophy in Frizzle fowl are consistent with those reported in our previous paper¹ that the heart rates of Frizzle fowl are more rapid than those of normal fowl. It would appear that this cardiac hypertrophy, as well as the tachycardia are conditioned only by the high metabolism of the Frizzle fowl.*

The fact that an increased metabolism alone may cause functional and organic changes in the heart (tachycardia and ventricular hypertrophy) is of theoretical interest, as well as of practical importance, particularly in respect to the cardiac disorders of hyperthyroidism. Other evidence is available that an increased metabolism may add to the work of the heart. Hall and Tainter¹² have shown that the administration of dinitrophenol, a drug that increases the metabolism without the intermediation of the thyroid gland, may cause a considerable increase in the volume output of blood per minute. Smith and MacKay¹³ fed albino rats active thyroid material, and found that when the basal metabolic rate is so varied, a linear relationship exists between the heart rate and the basal metabolic rate. They further found a direct relationship between food intake and heart weight and pointed out that "this strengthens the view that heart weight is directly related to total metabolism and hence to volume flow of blood." These observations suggest a close

* Experimental work now in progress confirms this conclusion.

analogy to our findings in Frizzle fowl in whom both food consumption and metabolism is greater than in normal chickens.¹ Simonds and Brandes¹⁴ noted cardiac hypertrophy involving all of the chambers in dogs that were fed large amounts of thyroid extract. Minot and Means¹⁵ showed that in chronic lymphatic leukemia, in which there is an increased metabolic rate unassociated with hyperthyroidism, the pulse rate is elevated, and that the hearts examined postmortem were on the average 75 grams overweight.

Summary. Frizzle fowl, a variety of chicken with scanty plumage and resultant high basal metabolism, permit the study of the effect of increased basal metabolism, as such, on the heart. The heart weights of 57 normal and 53 Frizzle fowl were determined by a modification of Müller's method. The ventricular weight relative to body weight of Frizzle fowl is significantly greater than that of normal fowl. Both ventricles share equally in this hypertrophy. These observations, together with our previous demonstration of the existence of more rapid heart rates in Frizzle fowl, indicate that an increased metabolism alone may cause functional and organic changes in the heart (tachycardia and ventricular hypertrophy). They suggest that in Graves' disease, the elevated metabolism, by increasing the work of the heart, directly contributes to the cardiac disturbances that are so commonly observed.

We wish to acknowledge the technical assistance of Mrs. Helen S. Boas.

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FAMILIAL CLEIDO-CRANIO DYSOSTOSIS.*

JULIANNA R. TATUM, M.D.,

PHYSICIAN-IN-CHIEF, PEDIATRIC OUT-PATIENT DEPARTMENT, PHILADELPHIA
GENERAL HOSPITAL, PHILADELPHIA, PA.

(From the Pediatric Out-patient Department.)

ALTHOUGH defective clavicles were described by Martin as early as 1765, it was not until 1897 that Marie and Sainton further described and named the defect Cleido-cranio Dysostosis.

In 1902 Paterson published observations to show that the clavicle is developed in two portions: the outer part ossifies in membrane before cartilage formation takes place, the inner ossifies in cartilage. The clavicle is the first bone to ossify in man. A center appears in the 5th week or earlier—before a cartilaginous basis has begun to form; Fawcett demonstrated an embryonic clavicle in a 17-cm. fetus. The pathogenesis of this condition is obscure. Jansen of Leyden in 1921 suggested that a small amniotic sac exerted pressure on the growing cells, and caused congenital defects according to the time this occurred, but of course the hereditary factor must be borne in mind. The defect in the clavicles may range from a break in continuity simulating an ununited fracture to complete absence of both bones.

The cranial vault and facial bones also often present abnormalities. There is an increase in girth and breadth of the skull giving a cephalic index greater than normal, while the facial measurements are below the average. The frontal and parietal eminences are unduly large, the sutures and anterior fontanelle remain open. The palate is highly arched, with a median furrow; the inferior maxilla is prognathous; the teeth are late in erupting and are incomplete and irregular in development and setting.

The phalanges are shorter than normal. There is frequently a spina bifida, and occasionally defects in the ribs and coccyx.

The height is below normal average giving the appearance of mild dwarfism. There is generally no disability from the defective clavicles, and rarely is pain caused by pressure of the clavicular stumps upon bloodvessels or nerves beneath.

The sex frequency is apparently equal. Fathers or mothers may transmit the condition to sons or daughters, and it may involve three or four generations. However, isolated cases are not rare.

Lues is not a causative factor, and associated diseases, such as tuberculosis, are negligible. Early rickets is found in some cases, although many are diagnosed as such before the true state is discovered.

* Read before The Philadelphia Pediatric Society, January, 1934.

Case Abstracts. CASE 1.—On February 6, 1933, Harry E. was brought to our clinic because he was thin and small for his age. He was a white boy, aged 7, height $41\frac{1}{2}$ inches, weight $38\frac{1}{2}$ pounds. He was pale but not acutely ill. Temperature 99 axilla, pulse 96, respirations 26. His head was large with prominent frontal and parietal eminences, and obvious grooves between these bones. The anterior fontanelle was open, and the vertex distinctly flattened. His face was small and receding in comparison with the cranium. The root of the nose was depressed and broad, the eyes set far apart, the lower jaw small and chin pointed.

The eyes, nose and ears were grossly negative. The palate was highly arched with a deep median furrow from the dental arch to the soft palate. The teeth were irregular and crowded; only 3 upper and 3 lower incisors were present and no permanent teeth had erupted. The tonsils were small and cryptic.



FIG. 1.—Two cases of cleido-cranio dysostosis. Harry, age 7 years, and his father, showing conformation of head and chest.

His chest was thin, with sloping shoulders and depressed sternum, especially at the xiphoid. No clavicles were palpable. The lower ribs were flared but there was no Harrison's groove or rachitic rosary. The scapulae were small but prominent. The lungs were resonant and breath sounds physiological. The heart was not enlarged; no murmurs elicited.

The abdomen was somewhat distended but soft. The liver was palpated 1 inch below the costal margin; no other organs or masses felt; no tenderness elicited.

His extremities were thin, no apparent disability or weakness, in fact, he was delighted to perform several contortionist stunts. His hands and feet stubby with short thumbs. No epiphyseal enlargement noted.

The Roentgen ray reports are as follows: "The right clavicle is entirely absent and only a small, rudimentary inner portion of left clavicle is visualized. Lung fields appear normal. Diaphragms are clearly visualized. The heart is not enlarged. The head is square-shaped. The anterior fontanelle is very wide and open. There is considerable thinning of the plate of the

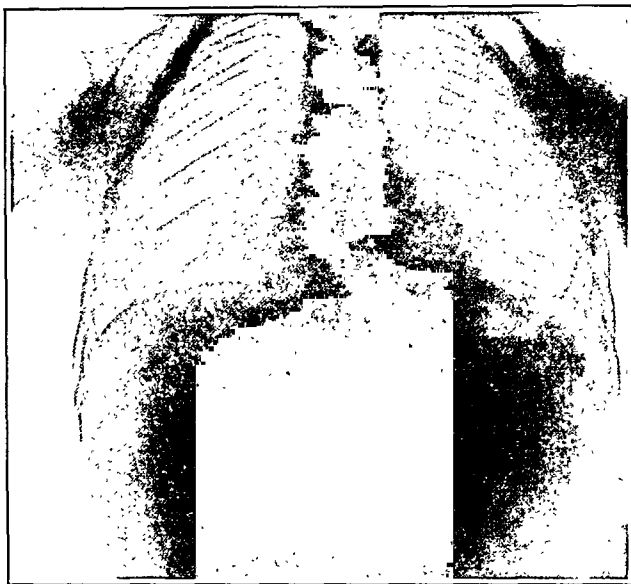


FIG. 2.—Roentgen ray of chest showing absence of right clavicle and rudimentary inner portion of left clavicle.

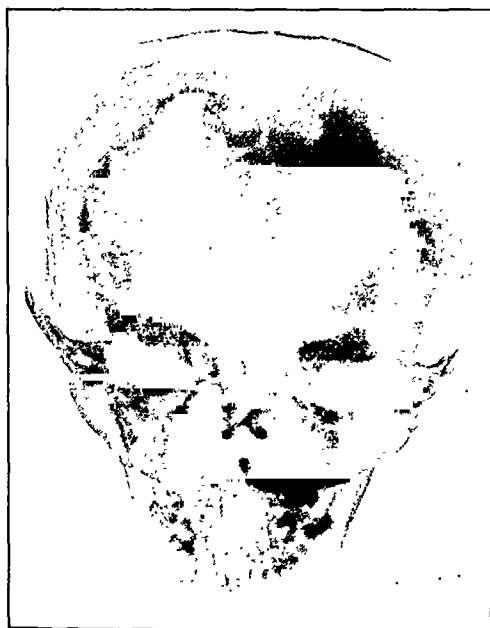


FIG. 3.—Roentgen ray of skull showing the open fontanelle, and non-union of the lower jaws at the symphysis.

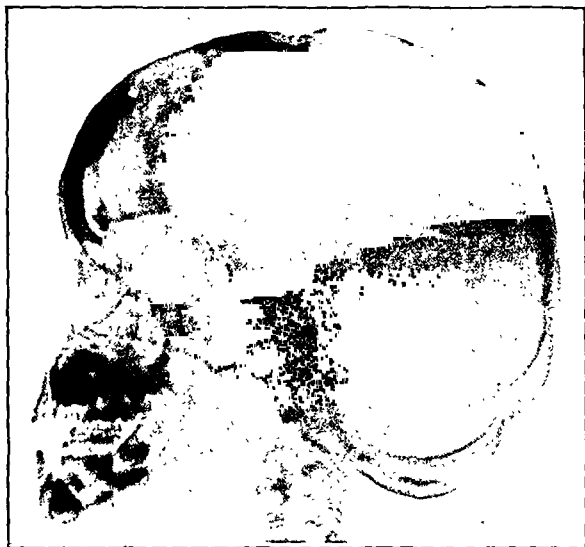


FIG. 4.—Lateral view of skull. This shows thinning of the plate of the frontal bone and widening of the sutures. The posterior portion of the skull drops below the usual level at the foramen magnum.

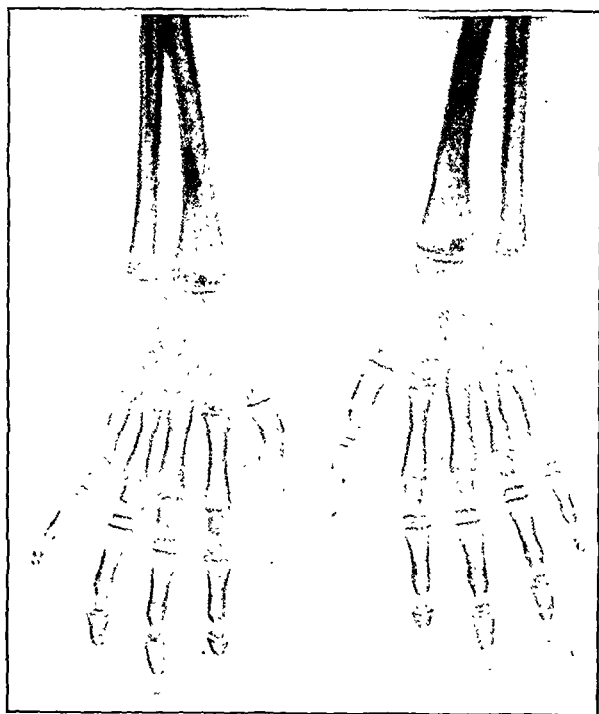


FIG. 5.—There is delayed development of the epiphyses of the carpal bones. The second phalanges of the index and little fingers are much shorter than normal and somewhat irregular in outline.

frontal bone. There is some widening of the sutures. The sella turcica appears normal. There is non-union of the lower jaws at the symphysis. The septum is considerably deflected to the right. There is delayed development of the epiphyses of the carpal bones. The second phalanges of the index and little fingers are much shorter than normal and somewhat irregular in outline." Diagnosis: Cleido-cranio dysostosis.

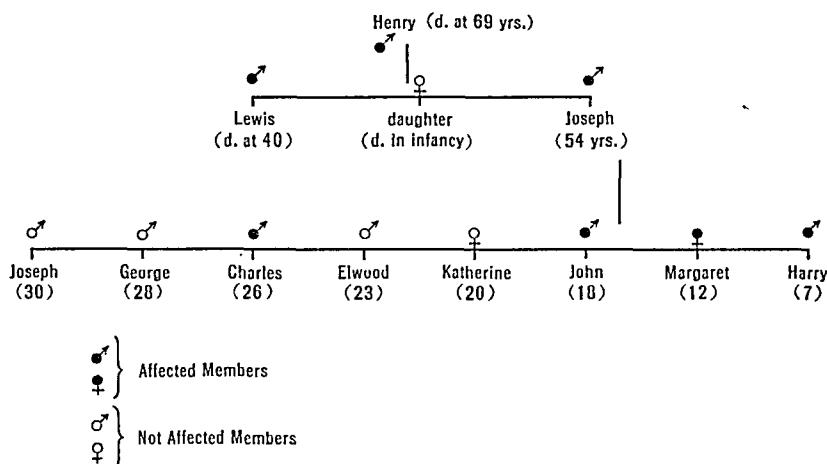
The blood calcium was 10.4 mg. per 100 cc.; phosphorus was 3.9 mg.

Past History. The patient was born in Philadelphia, full term, breech delivery. It is noted that he "was unable to move arms at all for 3 weeks. At 3 months he was admitted to the Babies' Ward of this hospital, because of failure to gain weight. His condition was immediately recognized and confirmed by Roentgen ray.

Much of the next 9 months was spent in the hospital. He gained weight slowly, reaching 14 pounds 12 ounces at 11 months. His skull increased to a circumference of 17 inches, with the anterior fontanelle large and tense, 3 by 4½ inches. Both the blood and spinal fluid Wassermann tests were negative, but he was given mercurial inunctions for 3 weeks. No other blood studies were made.

During 1927, 1928, and 1929, he was in fairly close touch with the clinic. In 1928 he had measles, pneumonia and pleurisy. His blood Wassermann test was again negative.

Chart 1.



The numbers in brackets show the present ages of living members.

At 2 years he weighed 22½ pounds; at 3, 25½ pounds; height 32 inches; at 4, 27 pounds, height not recorded; at 4¾, 29½ pounds, height 36 inches; at 6, 33 pounds, height 38 inches; at 7, 38½ pounds, height 41½ inches.

His present measurements are normal for 5 years.

This yearly increase in weight and height compares favorably with the normal average for ages 5 to 7 inclusive. Although he has always been short for his age, his weight has corresponded with his height according to Woodbury's tables (U. S. Dept. Labor).

Family History. Harry is the youngest of 8 siblings, all living. There have been no miscarriages nor stillbirths. Of the 8 children, 3 boys and 1 girl have defective clavicles, abnormal skulls, and malformed teeth. The father, Joseph, has rudimentary clavicles, and his brother, who died unmarried at 40, resembled him. The only other member of that generation

was a sister who died in infancy, condition unknown. Joseph's father had no clavicles, but nothing is known of his grandfather or of collateral branches of the family. Thus we have a history of 3 generations including 7 affected members. The family tree given below starts with the patient's grandfather and represents all of his descendants.

This family is of Pennsylvania stock, English descent, sturdy and able to do vigorous work. Joseph is a pipe fitter employed by the Westinghouse Company, his brother Lewis was a sailor and died by drowning. The father, 6 sons, and 1 of the 2 daughters, have been studied and the following data collected.

CASE 2.—Joseph, Sr., aged 54, shows that "both clavicles are rudimentary. The scapulæ are much smaller than normal, elevated; the chest is sort of barrel-shaped. The heart is not enlarged. Arch of aorta shows some evidence of arteriosclerosis, and the diaphragms are clearly visualized. The terminal phalanges are much smaller than normal. The epiphyseal line of the lower radius is still demonstrable but is united. All the carpal bones are present. The right frontal sinus is absent. The left one is somewhat smaller than normal. The septum is deflected to the left. There is no evidence of any unerupted teeth. The sella turcica is normal in shape and outline; not enlarged; no evidence of intracranial pressure. Suture lines are well outlined showing evidence of calcification." Roentgen-ray report March 13, 1933.

The blood Kahn test was negative; blood calcium, 10.2 mg. per 100 cc.; blood phosphorus, 3.3.

CASE 3.—Joseph, Jr., aged 30, known to medical clinic. "Typical neurasthenic." "The clavicles appear normal. The scapulæ are normally outlined; lung fields and cardiac silhouette are normal. The sella turcica is normal in size and outline. The suture lines are normal. There are several unerupted teeth in upper jaw; otherwise the maxillæ and mandible appear normal." (Roentgen ray report March 10, 1933.)

CASE 4.—George, aged 28, apparently normal white male. "The clavicles appear normal. Scapulæ are well-formed. The ribs and lung fields are normal. The heart is not enlarged. Sella turcica is normal in outline. There is no evidence of intracranial pressure. Suture lines appear normal. There are several unerupted teeth in the upper and lower jaws." (Roentgen ray report March 6, 1933.)

Blood calcium 13.8 mg. per 100 cc.; phosphorus, 2.5.

CASE 5.—Charles, aged 26, distinct type of cleido-cranio dysostosis. "This is another case of cleido-cranio dysostosis, described previously in other members of the family, showing abnormal development of the clavicles and under development of the scapulæ. Numerous unerupted teeth and non-union of the superior maxilla with an ectopic frontal suture, widening and squaring of the head and non-union of the suture lines. Sella is normal in size." (Roentgen ray report March 13, 1933.)

Blood calcium 10.7 mg. per 100 cc.; phosphorus 2.2.

CASE 6.—Elwood, aged 23, pipe fitter, apparently normal male. "The clavicles and bones of the skull do not show the typical findings we have noted in the other members of the family. Both clavicles are normally formed. There is no evidence of undescended teeth and the bones of skull appear normal." (Roentgen ray report March 13, 1933.)

Blood calcium 10.7 mg. per 100 cc.; phosphorus 2.5.

CASE 7.—John, aged 18, full term, normal delivery, birth weight 9 pounds. He had the usual childhood diseases. He first came to the clinic June 20, 1927, aged 12½ years.

The *physical examination* at that time is as follows: "Bosses enlarged. Nose stubby and bridge typically that of adenoids. Tonsils cryptic, not overly enlarged. Shoulders sloping. Funnel-chested. Slight marks of

rachitic rosary. Heart slight heave. No thrill. Marked impulse 5th and 6th interspace below nipple, size of a quarter. Soft blowing quality 1st sound. $P2 > A2$. Sinus arrhythmia. No murmurs. Chest and abdomen otherwise negative. Nails are some of them curved."

On September 26, 1927, there is a note "No complaints. . . . Edentulous and lacking outer half of clavicles."

June, 1927, weight 67 pounds; September, 1927, 70½ pounds; April, 1928, 73½ pounds; height 51 inches (normal height for 9 years).

Roentgen ray taken March 13, 1933: "This is another case of cleido-cranio dysostosis, described previously in the other members of the family, showing the abnormal development of the clavicles and underdevelopment of scapulæ. Numerous unerupted teeth and non-union of the superior maxilla with an ectopic frontal suture, widening and squaring of the head and non-union of the suture lines. Sella is normal in size."

Blood calcium 11.6 mg. per 100 cc.; phosphorus 2.8.



F.g. 6.—Margaret, age 12 years, showing eruption of permanent incisors behind deciduous teeth.

CASE 8.—Margaret, aged 12, height 55¼ inches, weight 102 pounds, short, obese, white girl not yet adolescent. Her head is large, with prominent frontal bosses and a broad low forehead. The anterior fontanelle is apparently closed. The eyes are set far apart, but otherwise grossly negative. The nose and ears are normal. The chin is small and pointed, the palate highly arched, with a deep groove from the incisors to the soft palate. The tonsils are small. The teeth are irregular, poorly formed and carious. The second set of incisors are erupting behind the deciduous teeth which are still present.

There is no cervical adenopathy, but the thyroid is palpable. Her chest is round and obese. There is a partial clavicle palpable on the left and a stub attached to the sternum on the right. The lungs are clear and the heart apparently normal. The abdomen is obese, no tenderness nor rigidity, no masses nor organs palpable. Her hands and feet are stubby, with short thumbs. There is no evidence of old rickets.

"There is only a small rudimentary portion of the right clavicle present, and a somewhat larger rudimentary clavicle on the left side. On the right side just the inner third is demonstrable and on the left side the inner two-thirds is visualized. The lung fields appear normal. Diaphragms are clearly visualized. The heart is not enlarged. The head is square-shaped. There is some widening of the sutures. The anterior fontanelle is still open.

There is considerable thinning of the vault in this area. There is non-ossification of the lower jaws at the symphysis. There is delayed dentition, and the terminal phalanges have a peculiar rounded effect. There is an ectopic suture in the frontal lobe." (Roentgen ray reports.)

Blood calcium 10.8 mg. per 100 cc.; phosphorus 4.5.

Margaret had a normal delivery at full term. Birth weight $8\frac{1}{2}$ pounds. She had the usual childhood diseases before she was 6, as well as diphtheria and pneumonia. She first came to the clinic in 1927 and was a fairly regular visitor for 3 years. Her most common complaint was nausea and vomiting with abdominal pain, and several times appendicitis was considered. Her Wassermann test was reported negative in both antigens. It is interesting that there is no mention of any bony abnormality during this period, although with 2 brothers both known to be without clavicles, attending clinic at the same time, it seems strange that it was unnoted. No Roentgen ray was taken at that time.

March 14, 1933, B. M. R., +18.

1927, weight 44 pounds, height not recorded; 1929, 52 pounds, height not recorded; 1930, 64 pounds, height 50 inches; 1933, 102 pounds, height $55\frac{1}{4}$ inches.

Discussion. Of the 144 cases reviewed by Stocks in 1925, not one mentions blood studies other than Wassermann tests. Fitchet, in 1929, gives the figures of blood calcium and blood phosphorus on 1 case and reports 2 other cases as being "within normal limits." Malmberg, in 1932, reports a sporadic case, with a blood calcium of 10.8 and blood phosphorus of 3.8, and quotes Klinke and Pahlke, who, in 1930, studied 2 cases with similar results.

These 4 cases are all that I can find in the literature on which blood studies have been reported. To these I have added the figures on our patients, which tally closely and I believe are significant. In children the normal blood calcium, according to Levinson, ranges from 10 to 11.5 mg. %, and the phosphorus from 4.8 to 6.8 mg. %. In these patients there is a decided lowering of the latter, while the calcium maintains a normal level.

TABLE 1.—BLOOD CALCIUM AND PHOSPHORUS FINDINGS IN 11 SUBJECTS.

Patient.	Children.	Age, years.	Blood calcium.	Blood phosphorus. (Normal 5 mg.)
1. Malmberg's case		3	10.8	3.8
2. Klinke and Pahlke's Case 1		$3\frac{3}{4}$	12.1	3.8
3. Case 2		$4\frac{3}{4}$	11.8	2.9
4. Fitchet's case		10	10.1	4.4
5. Harry		7	10.4	3.9
6. Margaret		12	10.8	4.5
<i>Adults.</i>				(Normal 3 mg.)
7. John		18	11.6	2.8
8. (Elwood)		23	10.7	2.5
9. Charles		26	10.7	2.2
10. (George)		28	13.8	2.5
11. Joseph, Sr.		54	10.2	3.3

The two patients in parentheses did not have the dysostosis.

Most of the children suffering with this condition are diagnosed as cases of rickets, for the clavicular defect is not apparent and the square head with prominent bosses is noticed at a glance.

Like many other defective conditions supposed to be rare until we look for them, cleido-cranio dysostosis probably is more common than we suspect. Much more study must be done before we can draw definite conclusions from this family, but I believe it significant that Harry's retardation of growth occurred within the first 2 years of life, and that there is a definitely low blood phosphorus.

If sporadic cases could be recognized early, and if affected families could be watched and possibly prenatal treatment given, perhaps as in rickets, we could alleviate the severity of the defects.

Summary and Conclusions. A case of cleido-cranio dysostosis is reported with Roentgen ray and blood chemistry studies. A family tree and brief notes on members of the immediate family are given. The blood phosphorus and blood calcium of these 7 individuals is compared with figures on similar cases given by other writers. The blood chemical findings in the adult members are normal, but the children have a normal calcium with a lowered phosphorus percentage.

Acknowledgment is made to the helpful coöperation of the Department of Radiology in the preparation of the Roentgen ray photographs, and to the Pathological Laboratories for the blood chemical examinations.

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SYMPATHOGONIOMA OF THE ADRENAL.

H. LeBARON PETERS, B.A., M.D.,
PATHOLOGIST,

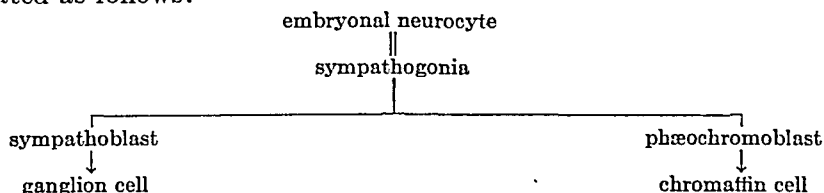
AND

BENJAMIN HORN, B.S., M.D.,
ASSISTANT PATHOLOGIST, BRIDGEPORT HOSPITAL,
BRIDGEPORT, CONN.

(From the Pathological Laboratory of the Bridgeport Hospital.)

SYMPATHOGONIOMA of the adrenal gland is a tumor growth originating in the adrenal medulla derived from the primitive cells of the sympathetic nervous system. Marchand, the first to describe an adrenal tumor (1891), suggested that tumors of the adrenal medulla might have their origin in the embryonic sympathetic nerve cells. In 1910, through the work of Wright¹ these tumors were called sympathetic neuroblastomas. Since then, several tumors of this type have been recorded in the literature. That these tumors are very infrequent is evident when we note that Saphir² reported his case as the only one in 3950 autopsies. Warthin³ did not even mention this type of tumor in reporting an analysis of 2000 cases of malignant neoplasms in the young at the University of Michigan. Also, Jacobsen and Hosoi⁴ reported only a single case from the Albany Hospital in the last 30 years, while our case is the first on record from this hospital in the last 25 years. In view of the above reports we may say that this type of adrenal tumor is relatively a rare occurrence; and because of the relative infrequency and the interesting features it presents, we add our case to the literature.

In the normal embryonal development of the sympathetic ganglia, the first and most undifferentiated cell arises from the primitive neural canal and is called the embryonal neurocyte. Its development into mature ganglion cells and chromaffin cells may be tabulated as follows:



A tumor arising from the sympathogonia is called a sympathogonioma, while a tumor consisting of sympathoblasts is a sympathoblastoma and a tumor arising from the ganglion cells is a ganglioneuroma. While such a nomenclature is useful in designating



FIG. 1.—Photograph of sympathogonioma of the right adrenal.

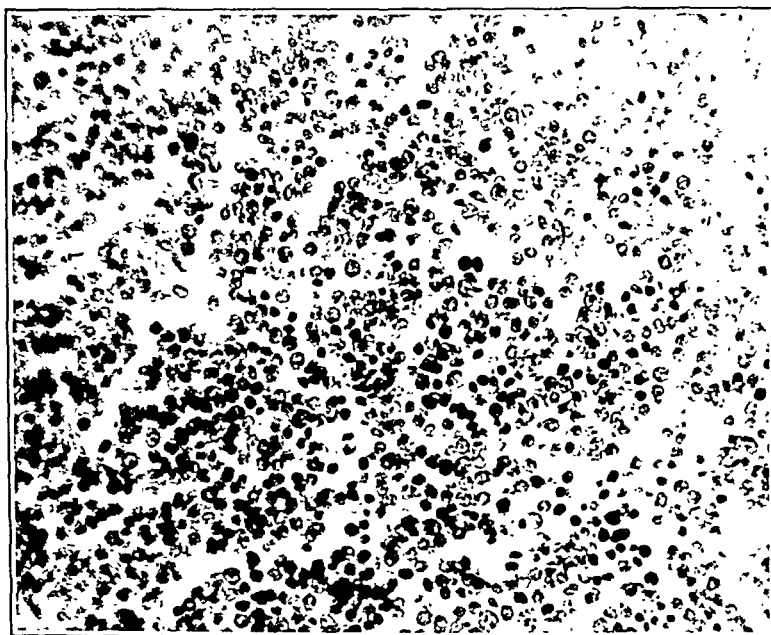


FIG. 2.—Microphotograph of sympathogonioma of adrenal showing the primitive sympathetic nerve cells. Hematoxylin-eosin stain. $\times 250$.

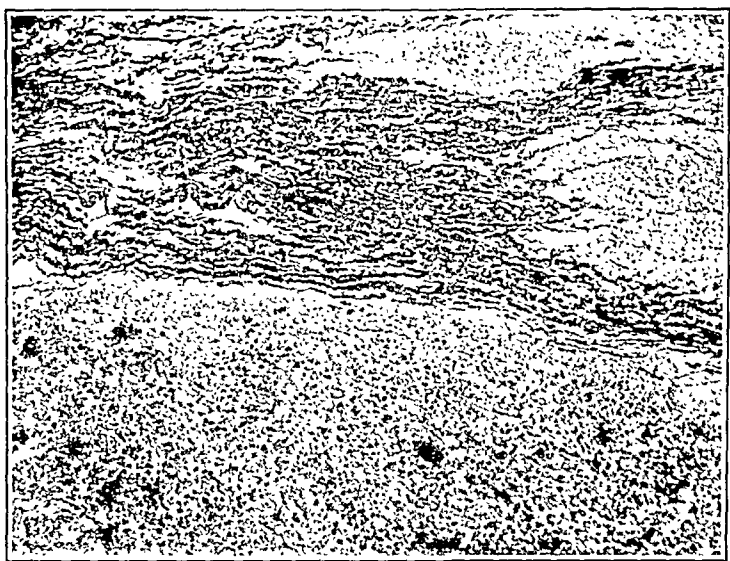


FIG. 3.—Microphotograph showing the bands of connective tissue between areas of densely grouped cells showing complete absence of intercellular stroma. Klarfield's stain. $\times 125$.



FIG. 4.—Microphotograph of the metastatic nodule in the liver showing the small round cell infiltration and necrosis of the immediate surrounding liver cells. Hematoxylin-eosin stain. $\times 125$.

sympathetic nerve tumors, in reality these growths almost always contain cells of the different stages of development. In the case we are reporting, the tumor showed a predominance of the more immature cells, the sympathogonia, with a very few scattered sympathoblasts. According to the classification proposed by Bielschowsky,⁶ we designate our tumor a sympathogonioma. Dr. H. M. Zimmerman of the Yale Medical School has confirmed this diagnosis.

In general sympathogonioma is most common in the newborn and the young but cases have been reported in adults by Ritter,⁵ Meltzer,⁷ and by Symmers.⁸ Being composed of primitive undifferentiated cells, the sympathogonioma is very highly malignant and metastasizes rapidly especially to the liver as was found in our case.

Grossly, the sympathogonioma tumors may or may not be encapsulated and are fairly soft in consistency. They may grow to the size of an apple and on section, the cut surface presents a variegated appearance showing areas of hemorrhage and degeneration. Metastases may appear in the mesenteric and retroperitoneal lymph nodes and bone in addition to the liver. Microscopically, the tumor consists of large numbers of small undifferentiated round cells with oval deeply staining nuclei, rich in chromatin and surrounded by a very delicate ring of cytoplasm. The cells may be arranged diffusely or in alveolar formation. In the metastatic lesions, the structure is composed mainly of small round cells.

Case Reports. D. P. B., a male child, 2 years of age, was admitted to the Pediatric service of Dr. C. V. Calvin on August 11, 1933 for listlessness and swelling of the abdomen. The past history and family history were essentially negative.

The present illness began 3½ weeks previously when the child became listless and developed a slight fever. Under the care of the family physician the child apparently improved for a few days, but again became listless. A few days before admission, the mother noticed that the child was slightly yellow and that the abdomen was getting larger. On admission, examination showed a fairly well-developed and fairly well-nourished white male child moderately pale and quite irritable. There was no general glandular enlargement. The lungs showed dullness on percussion over the right chest posteriorly from the level of the spine down, with diminution of the breath sounds. The heart was normal in size, regular, rapid rate of 140 per minute but no murmurs. The abdomen was markedly distended with prominence of the superficial veins of the skin. The liver appeared to be enlarged, the lower edge being palpated at the level of the umbilicus. There was a feeling of fullness on palpation in the right costovertebral area but no tenderness could be elicited. The extremities showed a slight edema from the toes up to the knees.

Course During Illness. The patient slept most of the time and when awake he was irritable, restless and refused to eat. The abdomen gradually increased in size with the accumulation of fluid. Because of the enlarged abdomen with ascites developing fairly acutely, an exploratory laparotomy was performed on August 19, through an upper right rectus incision and when the peritoneal cavity was opened, a great amount of straw-colored fluid escaped from the wound. The liver was found to be moderately enlarged but smooth. As the condition of the patient was critical, extensive exploration was not possible. The patient gradually became weaker and

soon after regaining consciousness from the anesthesia lapsed into coma and died the next day.

The temperature varied between 98° and 103°, the pulse between 110 and 160, and respirations around 36 per minute. Mantoux tests with 0.1 mg. and 1 mg. of old tuberculin were negative. Blood examination on August 11 showed R. B. C. 3,300,000, W. B. C. 6825 with Poly. 76%—Band forms 17%, S. L. 20%, Mono. 4%, Eos. 2%. Hemoglobin 52 (Sahli). Platelets 464,000. Icteric index 10. Another blood count 5 days later was essentially the same. Bleeding time 2 min. Venous coagulation time 5½ min. with clot retraction at 15 min. Blood Wassermann and Kahn tests were negative. Sedimentation time was 1 hr. and 25 min. Blood cultures showed no growth. The urine on repeated examinations showed a very faint trace of albumin. Roentgenologic examination on August 12 reported that the right dome of the diaphragm was elevated, the result of an enlarged liver.

Necropsy (restricted to the operative incision, done 1 hr. after death). On opening the incision a quart of blood-tinged fluid issued forth. The right dome of the diaphragm was at the level of the third rib in the mid-clavicular line, the left dome at the fourth intercostal space. The lower border of the liver extended 4 inches below the costal margin, was pale yellow and smooth, except for 2 very small white nodules about 1 cm. in diameter on the superior surface of the right lobe. The abdominal viscera appeared to be pushed forward by some mass deeper in the abdominal cavity. There were numerous small glands at the root of the mesentery, varying in size from 1 to 5 cm. in length, pale red and very soft in consistency. The spleen appeared to be normal. The liver when removed was enlarged, weighing 480 gm., capsule smooth and pale and except for the two small nodules on the superior surface showed no gross change. The left kidney was normal in size, pale red in color and weighed 68 gm. The left adrenal was normal in size and the cut surface showed no gross change. The right kidney was found to be compressed at the upper pole by a mass which replaced the right adrenal gland (Fig. 1). The mass measured 6 inches long, 4½ inches wide and 4 inches in depth. It was grossly nodular in appearance, grayish-yellow in color, and moderately soft in consistency. Attached to the posterior surface were numerous matted glands. On section, the cut surface of the tumor mass presented a variegated appearance consisting of reddish-yellow areas with parts showing hemorrhage and necrosis. Near the periphery, in some sections, could be seen portions of the yellow-brown structure of the adrenal cortex. The compressed kidney below the tumor mass showed no neoplastic involvement.

Sections of the tumor were stained with hematoxylin and eosin, Van Gieson's stain, Mallory connective tissue stain, Klarfeld's tannic acid silver carbonate stain and with Bielschowsky stain. Histological examination of the various sections showed that the tumor consisted mainly of small round cells about the size of small lymphocytes, with round deeply staining stippled nuclei and surrounded by very scant cytoplasm hardly discernible (Fig. 2). These cells are identical with the cells described by Bielschowsky as sympathogonia.

Scattered among these cells were seen some somewhat larger round cells with clearer vesicular nuclei. In the main, the tumor cells had no definite arrangement, lying diffusely in a very small amount of connective tissue stroma. Although the neoplasm had very little intercellular stroma, there were seen rather wide bands of connective tissue which subdivided it into zones of polygonal shape and various sizes. These bands were best seen in the Klarfeld's tannic acid silver carbonate stain (Fig. 3).

Bielschowsky preparations for axis cylinders did not reveal any such structures in the neoplasm. Nissl preparations to demonstrate tigroid

substance in the cytoplasm were also negative. These results indicated that this neoplasm was a very primitive one and the cells represented sympathogonia.

Histologic examination of the small nodule in the liver showed a small round cell infiltration with necrosis of the immediate surrounding liver cells (Fig. 4).

Summary. 1. Sympathogonioma of the adrenal gland is a rare tumor, consisting of the most primitive sympathetic nerve cells (sympathogonia).

2. A case of sympathogonioma of the adrenal is reported in a child aged 2 years with metastases in the liver and retroperitoneal lymph nodes, fatal within 5 weeks after the onset of illness.

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THE TREATMENT OF BICHLORID OF MERCURY POISONING: A STUDY OF 46 CASES.

BY WILLIAM B. PORTER, M.D.,

PROFESSOR OF MEDICINE AND CHIEF OF MEDICAL SERVICE,

AND

C. E. SIMONS, M.D.,

RESIDENT PHYSICIAN IN MEDICINE, MEDICAL COLLEGE OF VIRGINIA,
RICHMOND, VA.

(From the Hospital Division, Medical College of Virginia.)

THIS study is concerned with an analysis of 46 patients who gave conclusive histories of having taken orally corrosive sublimate and who were treated on the medical wards of this hospital from January 1, 1927 to December 31, 1933. Eleven additional patients seen during this period gave similar histories, but the subsequent data and their clinical behavior introduced reasonable doubt as to the accuracy of their statements and they were therefore discarded from this study.

The evaluation of any method of therapy in corrosive sublimate poisoning must be made with the full realization that there are concerned many factors which cannot be completely and adequately subjected to analysis. Comparative results are therefore not entirely trustworthy, yet the number of cases here studied is sufficient more

or less to eliminate the variable equations and the results obtained do indicate that the therapy adopted is superior in kind.

All of the patients were observed for a length of time sufficient for the ultimate outcome to be noted. There were only 3 deaths, a mortality of 6.5%.

The therapy was designed in the full realization that for the present there is not available a trustworthy antidote for mercury poisoning. In the light of this important fact we based our therapeutic technique upon the known effects of ingested mercury and the probable pathogenesis of the fatal sequelæ.

The corrosive effect of bichlorid of mercury on the gastro-intestinal tract initiates a physical and biochemical state similar in its essential nature to that seen in extensive cutaneous burns. At times the shock and circulatory depression is so severe that death occurs within a few hours; and while this is unusual, the development of renal insufficiency immediately after the taking of the mercury frequently occurs. One of our patients excreted no urine for 192 hr., the anuria having followed immediately the taking of the mercury. Recovery occurred despite the fact that a blood creatinin of 12.2 mg. per 100 cc. was reached before diuresis was established.

The renal insufficiency follows immediately upon ingestion of mercury in those patients who have taken large amounts of the substance and in whom the corrosive effects are severe. It is undoubtedly due in part to the direct action of mercury on the capillaries of the glomeruli, but is more largely due to the concentration of blood and the depletion of the electrolytes operating jointly with disturbance of blood flow induced by shock and possibly more specifically through the mechanism of the vasomotor innervation to the splanchnic and renal vessels.

After the first 24 hr., renal insufficiency is the most important complication and it is related directly to the lesions produced in the kidney by the absorbed mercury. These lesions consist mainly of extensive necrosis of the epithelial cells lining the convoluted tubules and the proximate convoluted segments are those most severely involved. The glomeruli appear normal except for varying degrees of congestion and occasional swelling and desquamation of the capsular epithelium. One finds a reasonable explanation for the escape of the glomeruli on the one hand and the severe necrosis of the tubular epithelia on the other in the high concentration of the glomerulus filtrate which occurs in the convoluted tubules. It is certain that mercury is excreted by the glomeruli and is dealt with by the tubules in the same fashion as other non-threshold bodies, and therefore reaches a high concentration in this area. Cushny¹ states that 1 liter of urine is formed from 63 liters of glomerulus filtrate and it is reasonable to assume that a much higher concentration exists in mercury poisoning where dehydration occurs rapidly and is at times severe. Fatal uremia appears during the "gray" stage of

mercury nephrosis in the large majority of those who succumb to uremia after the first 48 hr. During this period the necrotic cells are being crowded into the lumen of the urinary tubules by the rapid development of new epithelia. Mechanical blockage of tubules by cell débris and urinary casts conceivably could cause complete cessation of filtration by these glomeruli. The absence of dilatation of the glomeruli has been suggested as an argument against the obstructive mechanism of the uremia of mercury nephrosis. This objection does not appear reasonable in a condition so acute, and furthermore it is not tenable that dilatation could occur when the kidney, as the result of the diffuse pathologic processes, is tensely swollen in its capsule. If then renal insufficiency is caused by the effects upon the glomeruli of the mechanically obstructed convoluted tubules, it follows that consideration must be given to the use of measures which may prevent this complication.

The exact mechanism of the formation of urinary casts is not understood, yet it is known that they are composed of precipitated protein and varying amounts of epithelial cell débris. Meyler² believes that urinary acidity reduces the globulin fraction to its isoelectric point and that the precipitation of this protein forms casts. Whether or not this be entirely correct, it is nevertheless true that blood and tissue proteins are less soluble in acid urine which has a pH of approximately 5 than in urine alkaline to litmus which has a pH of approximately 7.8. The isoelectric points of serum albumin and serum globulin are pH 4.7 and pH 5.7 respectively. Their place of least solubility is around the average urinary acidity. These facts have suggested a reasonable basis for the forcing of fluids to increase the amount of glomerulus filtrate in an effort to prevent stasis; and for the use of sodium bicarbonate to maintain urine alkaline to litmus at the kidney level, and conceivably to modify cast formation in the urinary tubules.

In the early stages of poisoning there occurs blood concentration and a definite reduction of the electrolytes as indicated by the plasma chlorids.

In all of the patients of this series with a leukocyte count above 20,000 per c.mm. the red cell count was 5,000,000 or more per c.mm. In this same group the patients on whom plasma chlorid studies were made all were below normal, the lowest being 186 mg. per 100 cc.; the highest 420 (as sodium chlorid). These findings indicate the necessity for using a solution for the relief of dehydration and for the replacement of plasma electrolytes.

The colon is an important avenue for the elimination of mercury, and colitis occurring in mercury poisoning is due to the action of mercury on the epithelial lining of the gut, during the process of excretion. It is improbable that colitis can be prevented by colonic irrigation, yet it is conceivable that irrigations may prevent reabsorption of excreted mercury.

CHART I.—BICHLORID OF MERCURY POISONING.

ANALYSIS OF PATIENTS HAVING LEUKOCYTOSIS BELOW 20,000—NO DEATHS.

Race.	Sex.	Age.	HgCl., grams.	Time taken.	Time of vomiting.	Time of lavage.	Pharyngitis.	Epigastric burning.	Diarrhea.	Stomatitis.	White blood count (in thousands).	Urinalysis.					Blood chemistry.		Associated disease.	Accidental.	Suicidal.	Recovered.	
												Albumen.	Red blood cells.	White blood cells.	Casts, hyalin.	Casts, granular.	N. P. N.	Creatinin.	Plasma chlorids.				
W	F	20	45	9.15 P.M.	9.25 P.M.	10.00 P.M.	++	++	0	0	11.6	Tr.	80	80	0	0	42	?	?	0	Yes	No	Yes
W	F	21	6	10.00 P.M.	10.30 P.M.	11.15 P.M.	++	++	0	0	7.4	Tr.	80	80	0	0	42	?	?	0	0	Yes	Yes
W	M	23	10	6.00 P.M.	5.10 P.M.	7.15 P.M.	++	++	0	0	10.9	Tr.	80	80	0	0	38	?	?	0	0	Yes	Yes
W	F	28	6	5.00 P.M.	0	6.00 P.M.	++	++	0	0	9.0	Tr.	80	80	0	0	26	?	?	0	0	Yes	Yes
W	F	18	15	11.50 P.M.	0	12.25 A.M.	++	++	0	0	16.0	Tr.	80	80	0	0	34	?	?	0	0	Yes	Yes
W	F	25	7.3	8.30 P.M.	8.40 P.M.	9.00 P.M.	++	++	0	0	12.0	Tr.	80	80	0	0	20	?	?	0	0	Yes	Yes
W	M	26	6	2.30 P.M.	0	3.00 P.M.	++	++	0	0	14.5	Tr.	80	80	0	0	30	?	?	0	0	Yes	Yes
W	M	37	22	11.00 P.M.	10.45 A.M.	11.45 P.M.	++	++	0	0	7.2	Tr.	80	80	0	0	36	?	?	0	0	Yes	Yes
W	M	30	15	9.30 A.M.	0	11.00 A.M.	++	++	0	0	15.0	Tr.	80	80	0	0	34	?	?	0	0	Yes	Yes
W	M	38	7.3	2.30 P.M.	0	3.15 P.M.	++	++	0	0	17.0	Tr.	80	80	0	0	38	?	?	0	0	Yes	Yes
W	M	28	7.3	1.00 P.M.	1.10 P.M.	1.40 P.M.	++	++	0	0	13.0	0	0	0	0	0	33	?	?	0	Yes	No	Yes
W	F	20	3	7.30 P.M.	0	8.15 P.M.	++	++	0	0	10.8	0	0	0	0	0	29	?	?	0	Yes	No	Yes
W	F	41	20	6.00 P.M.	6.15 P.M.	6.30 P.M.	++	++	0	0	16.6	Tr.	80	80	0	0	42	?	?	0	0	No	Yes
C	F	33	15	12.00 M.	12.15 A.M.	1.30 A.M.	2	2	+	+	15.9	3+	+	30	0	2+	34	?	388	0	0	Yes	Yes
C	F	34	7.5	9.00 P.M.	9.10 P.M.	9.30 P.M.	++	++	0	0	10.8	0	0	0	0	0	32	?	?	0	0	Yes	Yes
W	M	25	15	6.00 P.M.	6.20 P.M.	6.45 P.M.	++	++	0	0	12.4	+	0	0	0	0	?	?	?	0	0	Yes	Yes
W	M	20	6	1.15 A.M.	1.30 A.M.	2.15 A.M.	++	++	0	0	6.8	0	0	0	0	0	38	?	?	0	0	Yes	Yes
W	M	43	3.5	12.30 A.M.	0	1.30 A.M.	++	++	0	0	7.3	0	0	0	0	0	28	?	?	0	0	Yes	Yes
W	M	19	35	9.30 A.M.	0	10.15 A.M.	++	++	0	0	6.8	0	0	0	0	0	34	?	?	0	0	Yes	Yes
W	M	43	7.3	6.30 A.M.	6.15 A.M.	7.15 A.M.	++	++	0	0	7.4	Tr.	80	80	0	0	32	?	?	0	0	Yes	Yes
W	M	43	7.3	9.00 P.M.	0	10.00 P.M.	++	++	0	0	4.2	Tr.	80	80	0	0	44	?	?	Pern. anem.	0	Yes	Yes
W	F	30	8.2	4.15 P.M.	0	4.40 P.M.	++	++	0	0	10.4	Tr.	80	80	0	0	39	?	?	0	0	Yes	Yes
W	F	23	In sol.	4.00 P.M.	0	4.30 P.M.	++	++	0	0	9.6	0	0	0	0	0	38	?	?	0	Yes	No	Yes
W	F	22	20	4.00 P.M.	0	4.30 P.M.	++	++	0	0	12.0	Tr.	80	80	0	0	38	?	?	Preg-nancy	0	Yes	Yes
W	F	33	5	?	0	30 min. later	++	++	0	0	8.6	0	0	0	0	0	30	?	?	0	0	Yes	Yes
W	F	29	11	3.00 P.M.	3.15 P.M.	3.30 P.M.	++	++	0	0	12.3	0	0	0	0	0	32	?	?	0	0	Yes	Yes
W	F	16	7.3	?	0	35 min. later	++	++	0	0	7.6	0	0	0	0	0	38	?	?	0	0	Yes	Yes
W	F	25	7.3	?	Immediately	15 min. later	++	++	0	0	9.0	0	0	0	0	0	38	?	?	0	0	Yes	Yes
W	F	19	7.3	10.00 A.M.	10.10 A.M.	10.20 A.M.	2+	+	0	0	8.4	0	0	0	0	0	36	?	?	0	0	Yes	Yes
W	M	26	15	8.00 P.M.	8.15 P.M.	8.30 P.M.	++	++	0	0	11.8	Tr.	80	80	0	0	34	?	?	0	0	Yes	Yes
W	F	18	15	10.30 P.M.	?	11.00 P.M.	++	++	0	0	12.4	Tr.	80	80	0	0	24	?	?	0	0	Yes	Yes
W	F	23	7	?	?	20 min. later	0	+	0	0	6.8	0	0	0	0	0	?	?	?	0	0	Yes	Yes

CHART II.—ANALYSIS OF A SERIES OF CASES OF BICHLORID OF MERCURY POISONING.

				Time of vomiting.	Time of lavage.	Pharyngitis.	Epigastric burning.	Diarrhea.	Stomatitis.	White blood count (in thousands).	Urinalysis.				Blood chemistry.			Associated disease.	Accidental.	Suicidal.	Recovered.	Died.	Remarks.																				
			HgCl ₂ , grains.	Time taken.							White blood cells.	Red blood cells.	White blood cells.	Casts, hyalin.	Casts, granular.	N.P.N.	Creatinin.	Plasma chlorids.																									
ANALYSIS OF FATAL CASES.																																											
W	M	34	45	7.00 P.M.	8.30 P.M.	4+	4+	4+	3+	42.0	2+	2+	0c	2+	2+	40 to 312	2.1 to 18.4	368 to 189	0	0	Yes	No	Yes	Death on 16th day; uremia and colitis.																			
W	F	18	40	11.15 P.M.	12 hr. later	2+	2+	2+	2+	52.0	2+	+	0	0	0	126	8.4	?	0	0	Yes	No	Yes	Death in 56 hr.; shock and uremia.																			
W	M	42	15	?	20 hr. later	+	+	3+	+	39.0	2+	+	+	+	2+	72 to 384	6.4 to 21.0	?	0	0	Yes	No	Yes	Death on 9th day; uremia and colitis.																			
ANALYSIS OF PATIENTS HAVING LEUKOCYTOSIS ABOVE 20,000 WITH RECOVERY.																																											
W	F	23	11	6.15 P.M.	6.45 P.M.	0	2+	0	+	20.1	Tr.	+	0c	0	0	42	?	?	?	0	0	Yes	Yes	No																			
W	M	31	9	1.00 P.M.	1.30 P.M.	+	2+	0	0	21.4	Tr.	0c	0c	+	2+	34	?	386	0	0	Yes	Yes	No																				
W	F	27	22	12.30 A.M.	?	3+	3+	0	+	24.6	+	+	0c	+	+	46	?	378	0	0	Yes	Yes	No																				
W	M	26	37	7.00 P.M.	7.15 P.M.	4+	4+	0	4+	26.0	2+	+	0c	+	+	62	4.4	312	0	0	Yes	Yes	No																				
W	M	48	25	11.30 A.M.	0	+	2+	0	0	24.0	+	0c	0	0	0	26	?	310	Pul. tb.	0	Yes	Yes	No																				
W	M	44	17	9.30 P.M.	9.45	+	2+	0	+	20.6	Tr.	+	0c	0	0c	64	?	?	0	0	Yes	Yes	No																				
W	M	27	5	2.00 P.M.	2.15 P.M.	+	+	0	+	20.4	2+	0c	4+	0c	+	39	..	388	"GC"	0	Yes	Yes	No																				
W	F	36	20	12.30 A.M.	?	2+	2+	+	2+	26.0	+	+	+	+	+	228	?	?	0	0	Yes	Yes	No	Alkali begun on 10th day.																			
W	M	21	22	8.30 P.M.	8.40 P.M.	+	2+	0	+	36.2	+	0c	0	0	0c	92	?	?	0	Yes	No	Yes	No																				
W	M	19	73	3.00 A.M.	3.15 A.M.	+	+	0	0	21.0	Tr.	0	0	0	0	38	?	?	0	0	Yes	Yes	No																				
W	F	20	30	3.00 P.M.	3.10 P.M.	+	2+	0	+	26.8	Tr.	0c	0	0	0	100	4.2	?	0	0	Yes	Yes	No																				

Three (3) deaths in 14 cases with a leukocyte count above 20,000. Percentage deaths, 21.43 per cent.

Obviously the prompt and thorough removal of the mercury from the stomach by gastric lavage is the most important procedure in reducing morbidity and mortality. For the lavage a saturated solution of sodium bicarbonate is used, the reason for this being that the albuminates formed from contact of the mercury with the gastric mucosa, ingested proteins and mucin are readily soluble in an alkalin solution and will consequently be more completely removed.

The outline of therapy which follows is that used routinely on the medical wards and in principle has been adhered to in every instance in the treatment of this series of cases of mercury poisoning. Any modification in details of treatment has been influenced by variations from the expected clinical course of patients and to the development of unusual complications.

CHART III.—SUMMARY OF RESULTS.

	White.		Negro.	
	Male.	Female.	Male.	Female.
Oldest	48 yrs.	36 yrs.	..	34 yrs.
Youngest	19 yrs.	16 yrs.	..	22 yrs.
Average age	29 yrs.	24 yrs.	..	28 yrs.
Number of cases	22	22	..	2
Deaths	2	1	..	0

Total number of cases, 46; total number of deaths, 3 (6.5%).

	Plasma non-protein nitrogen.		Colitis and uremia.	Salivation and alveolar necrosis.	Leukocyte count.	
	Above 50 mg. %.	Below 50 mg. %.			Above 20,000.	Below 20,000.
Number of cases	9.0	37.0	5.0	2.0	14.0	32.0
Per cent of cases	19.5	80.5	10.8	4.3	30.4	69.6
Deaths	3.0	0.0	3.0	0.0	3.0	0.0

Treatment in Detail. 1. Immediate gastric lavage with a saturated solution of sodium bicarbonate, temperature 100° F. This is continued until the return fluid is clear. The lavage is repeated every 12 hr. for the first 5 days and is continued over a longer period if the chemical analysis of the washings shows mercury.

2. Morphine sulphate is administered immediately after the primary gastric lavage. This is repeated at intervals dependent upon the degree of shock, vomiting and pain; but the principle should be to relieve discomfort, retching and shock.

3. Sodium bicarbonate, 500 cc. of a 5% solution, is given intravenously immediately after the lavage, and 1000 cc. of normal saline solution are administered subcutaneously. As long as vomiting persists the same amount of each solution is repeated every 12 hr.

4. Sodium bicarbonate 5 gm. is given orally every 3 hr. during the day and every 4 hr. during the night. The amount of bicarbonate may be varied provided the urine is kept alkalin to litmus.

5. The total daily fluid intake must be at least 5000 cc. for an adult, and this amount must be maintained by oral, subcutaneous or intravenous

route, dependent upon the ability of the patient to retain the substances taken orally. Preference is always given the oral method.

6. The daily diet is orange juice 500 cc., milk 1000 cc. and beta lactose 100 gm. One egg daily is added as soon as vomiting is controlled. The feedings should be given every 3 hr. If vomiting interrupts the feeding schedule, 10% glucose solution is given intravenously in amounts sufficient to maintain an intake of at least 1000 calories. The bicarbonate solution can be made with the glucose solution and the injection given by the intravenous "drip" method. After the first week adequate nutrition and medication are in some cases interrupted by the development of a severe stomatitis and esophagitis. In 2 of the patients of this series a gastrostomy was done and we feel that it was the deciding factor in recovery. All the food and medicine were given through the gastrostomy tube and only water was given orally.

7. A colonic irrigation, using 5% sodium bicarbonate solution is given daily and is continued until recovery is assured.

Discussion. In evaluating a therapeutic principle, conservatism guided by a critical assay of the variable actors is imperative lest credit be given where credit is not due. To conclude that alkalization is solely responsible for the results obtained in this series of cases would be but to add another to those errors which arise in the evaluation of therapeutic procedures. Manifestly early emesis, the presence of food in the stomach, and prompt and thorough gastric lavage were largely responsible for the low mortality and morbidity.

An analysis of the methods of treatment advocated by various writers shows in common the principle of elimination and the use of various substances which tend to promote alkalization. Evans³ in 1880 advocated alkalies in the treatment of mercury poisoning and Hirsch⁴ suggested sodium bicarbonate as an antidote for mercury. Weis⁵ emphasized the importance of alkalies and recommended sodium bicarbonate for gastric lavage. He based his therapy on the observations of MacNider⁶ which indicated that an "acid intoxication" was an important feature of bichlorid of mercury poisoning. However, when one reviews the various methods of treatment advocated he feels that there is little justification for their complexity. The efficiency of any therapy for a disease caused by the ingestion of a poisonous substance must rest primarily upon an efficient method for the prompt removal of the harmful material from the stomach. The method must be simple, the drugs used in the treatment easily obtainable, and in the absence of a known antidote the therapeutic technique must be designed so that the fatal sequelæ may be prevented. The measures used in the treatment of this series of cases seemingly met these requirements quite satisfactorily.

An analysis of Chart II shows that of the 11 patients with a leukocyte count above 20,000 per c.mm. who recovered, only 1 had symptoms indicating colitis and that of mild type and short duration. Only 4 had a plasma non-protein nitrogen as high as 50 mg.

per 100 cc. These data suggest that the therapy used modified or prevented the development of the kidney lesions responsible for renal insufficiency; and almost totally eliminated colitis.

The infrequent occurrence of true mercury stomatitis was especially striking. Stomatitis occurring immediately as a result of the corrosive effects of mercury was present in 15 patients, but only 2 patients developed the severe type with salivation and alveolar necrosis. It is interesting that both of these patients developed anuria immediately after taking mercury. In one of them anuria lasted 192 hr., and in the other 84 hr. Both patients recovered, although the stomatitis was complicated by severe esophagitis which necessitated gastrostomy.

The prognostic significance of the leukocyte count is emphasized by this series of cases. The 3 fatal cases had leukocyte counts above 35,000 per c.mm., and only 1 patient with a leukocyte count above 30,000 per c.mm. recovered.

Conclusions. 1. While there is no known specific antidote for corrosive sublimate poisoning, yet a therapeutic scheme which emphasizes the use of sodium bicarbonate solution for gastric lavage, for colonic irrigation, and for dosage in amounts sufficient to maintain urine alkaline to litmus apparently reduced the mortality and morbidity in this series of patients so treated.

2. A concept of the mechanism of renal insufficiency in mercury nephrosis is presented and a tenable explanation of the mode of action of alkalization in preventing uremia is offered.

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A STUDY OF AURICULAR FIBRILLATION FOLLOWING OPERATIONS FOR GOITER.

BY A. CARLTON ERNSTENE, M.D.,

AND

BERT E. MULVEY, M.D.,
CLEVELAND CLINIC, CLEVELAND, OHIO.

AURICULAR fibrillation is the most common cardiac irregularity observed in hyperthyroidism. In a considerable number of cases the arrhythmia first develops shortly after thyroidectomy, and it is with this postoperative complication that the present investigation

is concerned. The study is based on 405 consecutive cases in which thyroidectomy was performed. Of these patients, 192 had adenomatous goiter without clinical or laboratory evidence of hyperthyroidism, while the remaining 213 had hyperplastic or adenomatous goiter with hyperthyroidism. Sixteen patients with hyperthyroidism had auricular fibrillation before operation (7%). The arrhythmia also was present before operation in 2 individuals who had adenomatous goiter without hyperthyroidism. Auricular fibrillation developed after operation in 35 of the 387 patients who had regular rhythm during the pre-operative period. It seemed that analysis of these 35 cases might yield considerable information concerning the pathogenesis and clinical importance of postoperative auricular fibrillation.

Of the 35 patients 31 had hyperthyroidism. They constitute 16% of the 197 patients with thyrotoxicosis who had normal rhythm before operation. The other 4 individuals presented no evidence of hyperthyroidism. Of the 35 patients 27 were women and 9 were men. All were between the ages of 35 and 61 years, but only 5 were less than 40. The basal metabolic rates in the patients with hyperthyroidism ranged from +8 to +76%. In 11 individuals the rate was +20% or less, but 5 of these had received iodids or Lugol's solution before entrance to the hospital. The metabolic rates in the patients without hyperthyroidism were between -8 and +9%. In the patients with hyperthyroidism, symptoms had been present for 4 months to 8 years, with an average duration of 23 months. Nine patients had had symptoms for more than 30 months; 1 had had a thyroidectomy for hyperthyroidism 8 years before the present admission and had had a gradual recurrence of symptoms after 4 years. Of the 35 patients, the 27 who were able to estimate the duration of the thyroid enlargement had had it from 1 to more than 40 years. Only 3 of the 27, however, had had noticeable goiter for less than 5 years.

Palpitation and dyspnea on exertion had been noted by practically all of the patients, but none had had myocardial failure and none presented evidence of congestion in the pulmonary or peripheral circulation at the time of admission to the hospital. The clinical histories suggested that 2 of the patients with hyperthyroidism had had short paroxysms of auricular fibrillation in the past. Two patients had had rheumatic fever during adolescence, and 3 others had had frequent attacks of tonsillitis. In 5 patients, all with hyperthyroidism, the systolic blood pressure remained above 150 mm. and the diastolic pressure above 90 mm. throughout the period of observation. Several individuals had slight or moderate degrees of peripheral arteriosclerosis, but extreme sclerosis was not recorded in any instance. Slight enlargement of the heart, as estimated by physical examination and roentgenologic studies, was present in 4 patients. Seventeen had systolic murmurs over the cardiac apex

or pulmonic valve area, and in 3 of these there was a systolic murmur in the right second intercostal space. None had a diastolic murmur. One patient with hyperthyroidism had numerous premature beats during the pre-operative period. Electrocardiograms were made in approximately one-half of the cases. Slight or moderate degrees of left-axis deviation were observed occasionally, but the tracings usually were essentially normal. Krumbhaar,¹ however, observed either right or left axis deviation to be frequent in patients with hyperthyroidism.

Onset of Postoperative Auricular Fibrillation.—In 2 individuals, auricular fibrillation developed during the operation, and in 4 others it appeared within the first 23 hours after operation. In 23 of the 35 patients, the irregularity began between 24 and 59 hours after operation, while in 6 it developed between 60 and 120 hours after operation.

In all patients, auricular fibrillation appeared during a time when the temperature was elevated, and in a few, normal rhythm was reestablished as the temperature curve returned rapidly to normal. A number of patients, however, had only slight postoperative fever, and in a majority it was not possible to establish a relation between the course of the temperature curve and the duration of the arrhythmia.

In 3 patients in whom the irregularity developed during the first 23 hours after operation, normal rhythm was reestablished after 3 to 13 hours, only to be followed by a second paroxysm of fibrillation 20 to 46 hours later.

Duration of Postoperative Auricular Fibrillation.—The arrhythmia lasted for less than 24 hours in 18 of the 35 patients and in only 8 individuals did it persist for more than 48 hours. The longest duration observed was 8 days.

Symptoms. Several patients complained of palpitation during the period of fibrillation, and in 4, slight or moderate dyspnea also was noted. In 1 individual, whose arrhythmia lasted 74 hours, râles developed over the bases of the lungs and moderate edema appeared over the lower back.

Type of Goiter. Pathologic examination of the surgical specimens from the 213 patients with hyperthyroidism revealed hyperplastic goiter in 117 instances, combined hyperplastic and adenomatous goiter in 17, colloid goiter with multiple adenomata in 62, colloid goiter in 9 and adenomatous goiter in 8. In the 31 individuals with hyperthyroidism in whom auricular fibrillation developed after operation, the specimen revealed hyperplastic goiter in 9 instances, hyperplastic and adenomatous goiter in 2, colloid goiter with multiple adenomata in 18, colloid goiter in 1 and adenomatous goiter in 1. In all 4 cases in which postoperative fibrillation developed in patients without hyperthyroidism, pathologic examination showed colloid goiter with multiple adenomata.

Discussion. Comparison of the patients who had postoperative auricular fibrillation with those in whom the cardiac rhythm remained regular revealed no differences that might have been used to forecast the development of auricular fibrillation after operation. Studies by several investigators^{2,3} have demonstrated that the incidence of auricular fibrillation during hyperthyroidism is more directly related to the age of the patient than to any other measurable factor. The arrhythmia is observed infrequently in thyrotoxic individuals less than 40 years of age. The duration of clinical hyperthyroidism is a less important contributory cause and the degree of elevation of the basal metabolic rate is of little significance.^{2,4} The results of the present study indicate that the factors which predispose to the development of postoperative auricular fibrillation are the same as those that govern the occurrence of the arrhythmia in hyperthyroidism before operation. In postoperative auricular fibrillation, however, an additional stimulus connected with the operation or the early postoperative course is necessary to initiate the arrhythmia.

Segall and Means⁵ demonstrated that the metabolic rate is increased to a variable but usually considerable degree during the first few days after subtotal thyroidectomy in patients with hyperthyroidism. They believe that the rise is to be explained largely as the result of fever and emotion. It is probable that this increased rate of metabolism and the consequent increased load upon the heart are the essential factors responsible for the initiation of postoperative auricular fibrillation. The same factors may also control the duration of the arrhythmia. It must be emphasized, however, that the irregularity may occur in individuals in whom the postoperative reaction and elevation in temperature are of mild degree.

Postoperative auricular fibrillation is more common both relatively and absolutely in patients with adenomatous goiter than in those with hyperplastic goiter.⁴ This cannot be accounted for entirely by differences in the ages of individuals belonging to the two groups. In the present series, 41 patients with hyperplastic goiter and normal rhythm before operation were 45 years of age or more. Of this number, 5 had postoperative auricular fibrillation, an incidence of 12%. Thirty patients with hyperthyroidism, colloid goiter with multiple adenomata and normal rhythm before operation were 45 years of age or more. Postoperative auricular fibrillation occurred in 11 of these, an incidence of 37%. The long duration of thyroid enlargement in the majority of patients with adenomatous goiter suggests an explanation for the more common occurrence of postoperative fibrillation in this group. It is possible that many of these patients have experienced repeated or prolonged periods of low-grade, unrecognized hyperthyroidism before the appearance of symptoms of sufficient severity to necessitate seeking medical advice. Such subclinical thyrotoxicosis might favor the

gradual development of myocardial damage and thus predispose to the development of postoperative auricular fibrillation.

The occurrence of auricular fibrillation after thyroidectomy in 4 patients with no symptoms or signs of hyperthyroidism is of considerable interest. Means⁶ recently has emphasized the diagnostic value of observing the effect of iodine on the basal metabolic rate of individuals with obscure hyperthyroidism. It would have been desirable to have made such studies in these patients, for otherwise the possibility of masked thyrotoxicosis cannot be excluded absolutely.

The development of auricular fibrillation after operations for goiter generally is a complication of but little clinical importance. The irregularity usually lasts for less than 48 hours and rarely causes circulatory embarrassment. Normal sinus rhythm almost always is reestablished spontaneously. In all but a few cases, no treatment is necessary. It has been our practice, however, to begin gradual digitalization with the onset of the arrhythmia so that the complete effect of the drug can be obtained more readily in the rare instances in which mild congestive failure does develop. If the arrhythmia should persist for more than 1 week, quinidin may be used to restore normal rhythm.

Summary and Conclusions. 1. Sixteen (7%) of 213 patients with hyperthyroidism had auricular fibrillation during the pre-operative period; while postoperative auricular fibrillation developed in 31 (16%) of the 197 who had normal rhythm before operation. The arrhythmia was present before operation in 2 of 192 individuals who had adenomatous goiter without hyperthyroidism and developed after operation in 4 other patients in this group.

2. The age of the patient, type of goiter and duration of hyperthyroidism appear to be the most important factors predisposing to the development of postoperative auricular fibrillation. The degree of elevation of the basal metabolic rate is of little significance. The immediate increase in the rate of metabolism following operation probably is the essential factor responsible for the initiation of the arrhythmia.

3. Postoperative auricular fibrillation is more common in thyrotoxic patients with adenomatous goiter than in those with hyperplastic goiter. This difference cannot be explained entirely by differences in the ages of individuals belonging to the two groups. The long duration of thyroid enlargement in the majority of patients with adenomatous goiter may favor the gradual development of myocardial damage, possibly as the result of repeated or prolonged periods of low-grade, unrecognized hyperthyroidism.

4. Postoperative auricular fibrillation generally begins during the first 60 hours after operation. It rarely causes circulatory embarrassment, and normal rhythm usually is reestablished spontaneously within 48 hours.

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THE ELECTROCARDIOGRAPHIC CHANGES PRODUCED BY INJURIES OF VARIOUS PARTS OF THE VENTRICLES.*

BY HERMAN KOREY, B.S.

STUDENT ASSISTANT,

AND

LOUIS N. KATZ, M.D.,

PHYSIOLOGIST AND DIRECTOR OF CARDIOVASCULAR RESEARCH, MICHAEL REESE
HOSPITAL; ASSISTANT PROFESSOR OF PHYSIOLOGY, UNIVERSITY
OF CHICAGO, CHICAGO, ILL.

(From the Cardiovascular Laboratory, Department of Physiology, Michael Reese Hospital, and the Department of Physiology, University of Chicago.)

CERTAIN investigators have claimed that the electrocardiographic changes following recent coronary occlusions can determine the location of the resulting myocardial infarctions. Thus, Barnes and Whitten¹ reported that typical alterations of the *Q-R-S-T* complex occur in infarction of the left ventricle; an infarct in the anterior wall of the left ventricle producing a curve which belongs to the T_1 type of Parkinson and Bedford's classification²; and one in the posterior wall, a T_3 type of curve. However, Gilchrist and Ritchie³ in their review of the literature of proven cases of recent coronary occlusion concluded that the available evidence did not lend support to the idea that the form of the electrocardiogram can be regarded as a definite localizing sign of infarction. This deduction is supported by the work of Saphir, Priest, Hamburger and Katz⁴ and by analysis of the autopsied cases reported recently by Wilson and his coworkers⁵ and by Wood, Bellet, McMillan and Wolferth.⁶ While Wilson *et al.*⁵ in their recent article stated that the location of the infarct plays an important rôle in determining the form of the ventricular complex, they nevertheless admit that many puzzling cases are met with when one attempts to correlate the electrocardiogram with the location of the infarct.

Barnes and Mann⁷ claimed that in the dog following coronary ligation, a T_1 type of change occurred when the infarct involved the left ventricle and a T_3 type of change when it involved the right

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ventricle. Other investigations are not in accord with this interpretation. Thus, Feil, Katz, Moore and Scott,⁸ Wolferth and Wood⁹ and Harris *et al.*,¹⁰ found a noticeable variability in the type of change in the electrocardiogram following ligation of the anterior descending branch of the left coronary artery. The first two groups of investigators observed that in some instances ligation of this branch of the coronary artery produced no changes in the electrocardiogram taken with the standard three leads.

Other attempts have been made to correlate the location of myocardial lesions with the type of change seen in the electrocardiogram. Thus, Crawford *et al.*¹¹ reported that, with rare exceptions, lesions produced in the anterior left ventricle of the cat's heart by means of a cautery gave rise to a T₁ type of electrocardiogram and located in the posterior left ventricle gave rise to a T₃ type of curve. A similar result was reported in the dog by Meek and his collaborators¹² using radon lesions, only one exception being found (a lesion in the posterior left ventricle failed to cause any change.) Meek *et al.*¹² further reported that lesions in the anterior wall of the right ventricle caused either no change or a T₁ type of electrocardiogram, and that lesions in the posterior wall of this ventricle had variable results. Robb¹³ recently concluded that the type of electrocardiographic changes following myocardial lesions was determined by the group of muscle bands in which the lesion was produced. She reported that the superficial bulbospiral, deep bulbospiral, superficial sinospiral and the deep sinospiral bands each produces its own characteristic changes. Fowler, Rathe and Smith¹⁴ found no correlation between the type of electrocardiogram and the location of the infarcts produced by tying small branches of the coronary arteries. It will be seen from the diversity of opinions expressed in the literature that the issue is not yet settled regarding the effect of the location of myocardial lesions on the electrocardiogram.

The present investigation was undertaken in an attempt to see whether or not injury and death of small sharply localized regions of heart muscles would produce characteristic alterations depending on the location of the lesion. For this purpose the ventricles were arbitrarily subdivided into 10 regions (Fig. 1). In order to make the results as clear as possible and to avoid the fluctuations in contour which occur from day to day in long term experiments because of the loose fixation of the dog's heart in the chest (Soskin, Katz and Frisch¹⁵), the destruction of muscle was produced as rapidly as possible and the changes followed for the first few hours.

Method. Dogs under morphin and sodium barbital anesthesia were used. The anterior chest wall was removed and artificial respiration instituted. The heart was placed in a snug cradle by suturing the split pericardium to the sides of the thorax, thus avoiding disturbing changes in position of the heart. The anterior chest wall was then replaced in order to restore approximately the usual chest contacts with the heart. A control electrocardiogram was recorded with the standard three leads, electrodes

TABLE 1.—SUMMARY OF DATA.

Exp. No.	Location of lesion.	Size of lesion.			T type of change.						Change in Q-R-S complex. Shift in electrical axis.†	Remarks.
		Endocardium mm.	Myocardium mm.	Epicardium mm.	Early.			Late.				
					Type	Degree	Time maximum change min.	Type	Degree	Time maximum change min.		
1	L. vent. ant. apex	8 ²	22 ²	15x6	T _s *	+++	1	T _s	++	240	Smaller L1, inverted L2 and 3. (Left)	Ventricular extrasystoles and paroxysmal tachycardia.
2	"	10 ²	14 ²	8x1	T _n *	+++	2	T _n	+++	240	Smaller all leads	
3	"	3 ²	25 ²	18x8	T _s	++	2	T _n	++	240	Inverted L1, diphasic L2 and L3	
4	"	2 ²	10 ²	15x3	T ₁	+	0	0		
5	L. vent. ant.	0	6 ²	6 ²	T ₁	+	1	0	Inverted L1 (right) Diphasic L2 and 3	
6	"	0	10 ²	5 ²	T ₁	+	1	T ₁	+	120		
7	mid.	0	8x15	0	T ₁	+	120	0		
8	"	0	15 ²	7x5	T _p	+	2	T ₁	+++	120		
9	"	±:	15 ²	10x2	0	T ₁	+	240	Q ₁ and 2 developed Smaller all leads Smaller L3. Q ₂ developed (left) Q ₂ and 3 developed Early inverted L1, later inverted L3 (right and left) Q ₂ and 3 developed Smaller all leads	
10	"	0	20x8	3x2	0	0		
11	"	0	10x6	0	T ₃	++	1½	0		
12	L. vent. post.	0	8 ²	0	0	0		
13	apex	0	20 ²	10x4	T ₃	++	2	T ₃	+++	240	Smaller L3. Q ₂ developed (left)	
14	"	±	20x7	0	T ₃	+++	2	T ₃	++	240	Q ₂ and 3 developed	
15	"	20x8	15x8	±	T _n	+	2	T _n	+	240	Early inverted L1, later inverted L3 (right and left)	
16	L. vent. post.	0	14 ²	10x8	T ₃	+	2	T ₃	+++	240	Q ₂ and 3 developed	
17	mid.	2 ²	30 ²	11x6	T ₃ *	+++	2	T ₃	+++	240	Smaller all leads	
18	"	2 ²	40 ²	12x10	T ₃ *	+++	2	T _n	+++	120	Inverted L1. Q ₁ developed (right)	
19	L. vent. post.	3 ²	38 ²	10 ²	T ₃	++	2	T ₃	+	120	Q ₂ and 3 developed	
20	base	0	14 ²	14x8	T ₃	++	2	T ₃	+	120	Smaller L3 (left)	
21	"	0	15x7	0	T ₃	+	10	T _n	+	120	Smaller L3 (left)	
22	"	0	15 ²	10 ²	T ₃	++	2	T ₃	+	240		
23	R. vent. ant.	3 ²	9 ²	8x3	0	0		
24	mid.	10 ²	11 ²	11x6	T _p	++	2	T ₁	+++	240		
25	"	0	12 ²	4x7	0	0	Larger L1, smaller L3 (left)	
26	"	10 ²	19 ²	15x5	0	0	Q ₁ developed	
27	R. vent. ant.	18 ²	31 ²	20x4	0	T ₁	+	240		
28	base	1 ²	15 ²	10x1	T ₁	+	10	T ₁	+++	240		
29	"	5 ²	25 ²	8x5	T ₃	+	2	T ₃	+	240		
30	"	20 ²	30 ²	24x5	T _p	+	2	T _p	+	120	Q ₂ disappeared	
31	"	2 ²	15 ²	10x5	T ₁	+	2	T ₁	++	120	Occasional ventricular extrasystoles.	
32	"	0	25x5	15x4	T _p *	++	2	T _p	++	240		
33	R. vent. post.	2x3	25 ²	25x5	T ₃	+	2	T ₃	++	240		
34	mid.	0	25 ²	25x8	T ₁	++	2	T ₁	+	120		
35	"	0	20 ²	15x4	T ₃	+	2	T _n	+++	240	Larger L1 and 2 (left) Q ₂ and 3 developed Smaller L3 (left) Temporarily smaller L1 (right)	
36	"	12x5	22 ²	20x6	T ₃	+	2	T ₃	+	240	Smaller L1, larger L2 and 3 (right)	
37	"	15x13	18 ²	18x8	T ₃	++	2	T ₃	+	240	Smaller L1 and 2 negative L3	
38	"	25x7	26 ²	22x6	0	0	Larger L1 (left), Q ₂ and 3 developed. Smaller L2 and 3 (left) Smaller and later inverted L3 (left) Taller L2 and 3 (right)	
39	"	0	15x5	10x2	0	T ₃	+	240		
40	R. vent. post.	2 ²	22 ²	20x7	0	T _p	+	240		
41	base	2 ²	18 ²	12x4	T ₃	+	2	T ₃	++	240		
42		10x17	15 ²	12x2	0	T ₃	+	120	Taller L2 and 3 (right)	
43		0	20 ²	13x2	T ₃	+	2	T ₃	+++	120		
		R. endo-cardium	Myo-cardium	L. endo-cardium								
44	Vent. sept. ant.	0	20x30	0	T ₁	+	120	T ₁	++	240	S ₂ and 3 appeared Smaller L3, S ₂ and 3 developed (left) S ₂ and 3 developed S ₃ developed	
45	mid.	0	20 ²	±	T ₁	+	2	T ₁	+	240		
46	"	0	25x8	15x8	0	0	Occasional ventricular extrasystoles.	
47	†	0	10 ²	0	T _p	+	120	T _p	+	240		
		Endo-cardium 0	Myo-cardium 25 ²	Epi-cardium 20 ²								

* Curve has monophasic appearance.

† The shift in axis is given in parenthesis.

‡ Location of lesion is in this instance in the interventricular septum anterior middle and left ventricle anterior middle. Note: As shown in Fig. 1 the apex of the dog's heart is occupied entirely by the left ventricle and the basal portion anteriorly entirely by the right ventricle.

A few spots show.

of German silver having been inserted beneath the skin of the two fore limbs and the left hind limb. The anterior chest wall was then temporarily removed and 1 cc. of 95% alcohol solution was injected into a predetermined area of the ventricular myocardium. (When injecting the interventricular septum the quantity of solution used was increased to 5 to 10 cc.) Care was taken to avoid involving the superficial coronary vessels. Following the alcohol injection the anterior chest wall was again replaced and a second electrocardiogram was taken as soon as possible ($\frac{1}{2}$ to 1 min.). Subsequent records were taken at approximately 2 min., 10 min., 1, 2 and 4 hr. after the injection. Following the last record the heart was removed. The position and area of the lesion produced by injection was then measured and its relation to the endocardium and epicardium was determined in the fresh specimen. These observations were later checked with Dr. M. Corrigan of the Department of Pathology, in the formaldehyde preserved specimen. The injected area was easily identified grossly both in the fresh and preserved specimens as a well-defined circumscribed region showing some hemorrhage. These lesions do not resemble infarcts histologically because the alcohol appears to act as a fixative, preserving the cytologic appearance for the few hours before the whole heart is fixed.

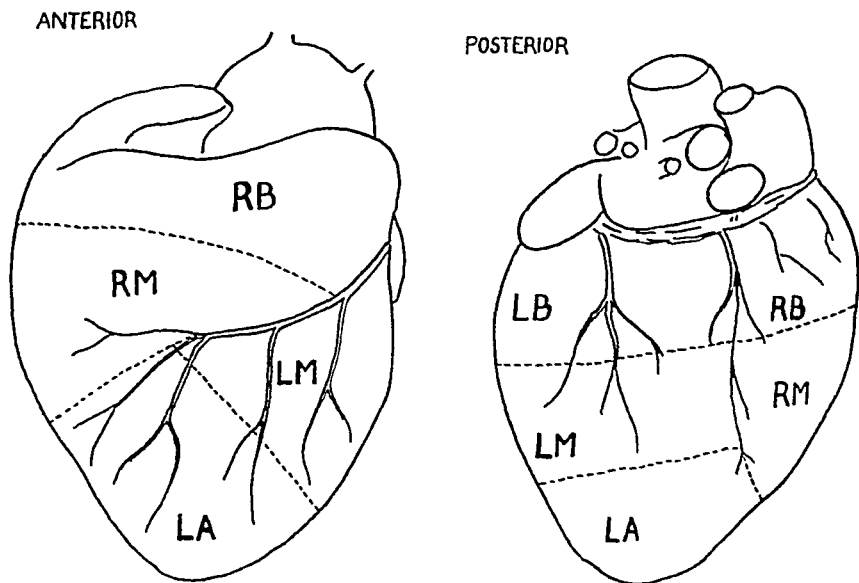


FIG. 1.—Diagram showing the subdivisions of the anterior and posterior surfaces of the heart used in this analysis. LA., LM., LB., represent respectively apex, middle and base of the left ventricle. RM., RB., represent respectively middle and base of the right ventricle.

Results. The data of the 47 experiments are summarized in Table 1 and illustrative records of typical results are shown in Figs. 3 to 8. The subdivisions of the heart surfaces used are shown diagrammatically in Fig. 1. In addition the anterior interventricular septum was also injected. Fig. 2 shows the result in a control experiment in which 1 cc. of alcohol was injected into the left ventricular cavity. The electrocardiograms in this experiment showed no significant changes during the 4-hour period.

From Table 1 it will be seen that deep negative Q waves frequently developed in one or more leads following the production of the myocardial lesion (Figs. 6 and 7). In other experiments deep, negative S waves developed (Fig. 5). In many instances the electrical axis of the heart showed a noticeable shift following the production of the myocardial lesion (Fig. 4). Occasionally the amplitude of the Q - R - S complex decreased in all leads (Fig. 3).

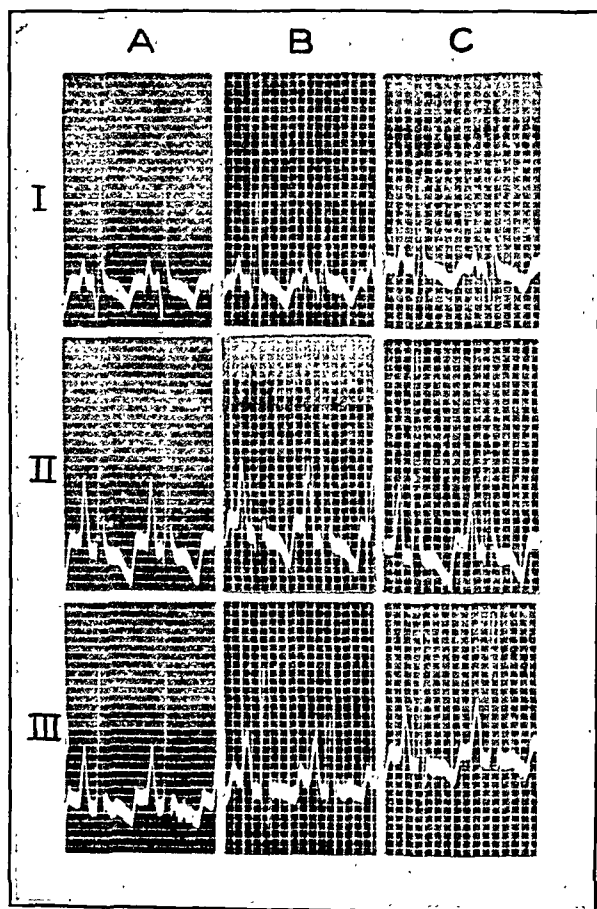


FIG. 2.—Electrocardiograms, standard three leads, in the control experiment in which 1 cc. of 95% alcohol was injected into the left ventricular cavity. Segment A was taken before the alcohol injection; Segment B, 2 min., and Segment C, 4 hr. after the alcohol injection.

The appearance of a typical Q type could not be predicted from the location of the myocardial lesion. When the Q type was classified according to the scheme of Wilson *et al.*, no constant correlation could be made between the location of the myocardial lesion and the Q type when it developed. (Compare experiment 16 with experiment 18). In this series, however, the anterior septal lesions were followed, without exception, by a Q_1 type of curve. The occurrence

of a shift in the electrical axis could not be predicted; nor, when it occurred, could it be accurately correlated with the location of the myocardial lesions. (Compare experiments 33, 34 and 39 with experiments 35 and 36, and experiments 40 and 41 with experiment 43.)

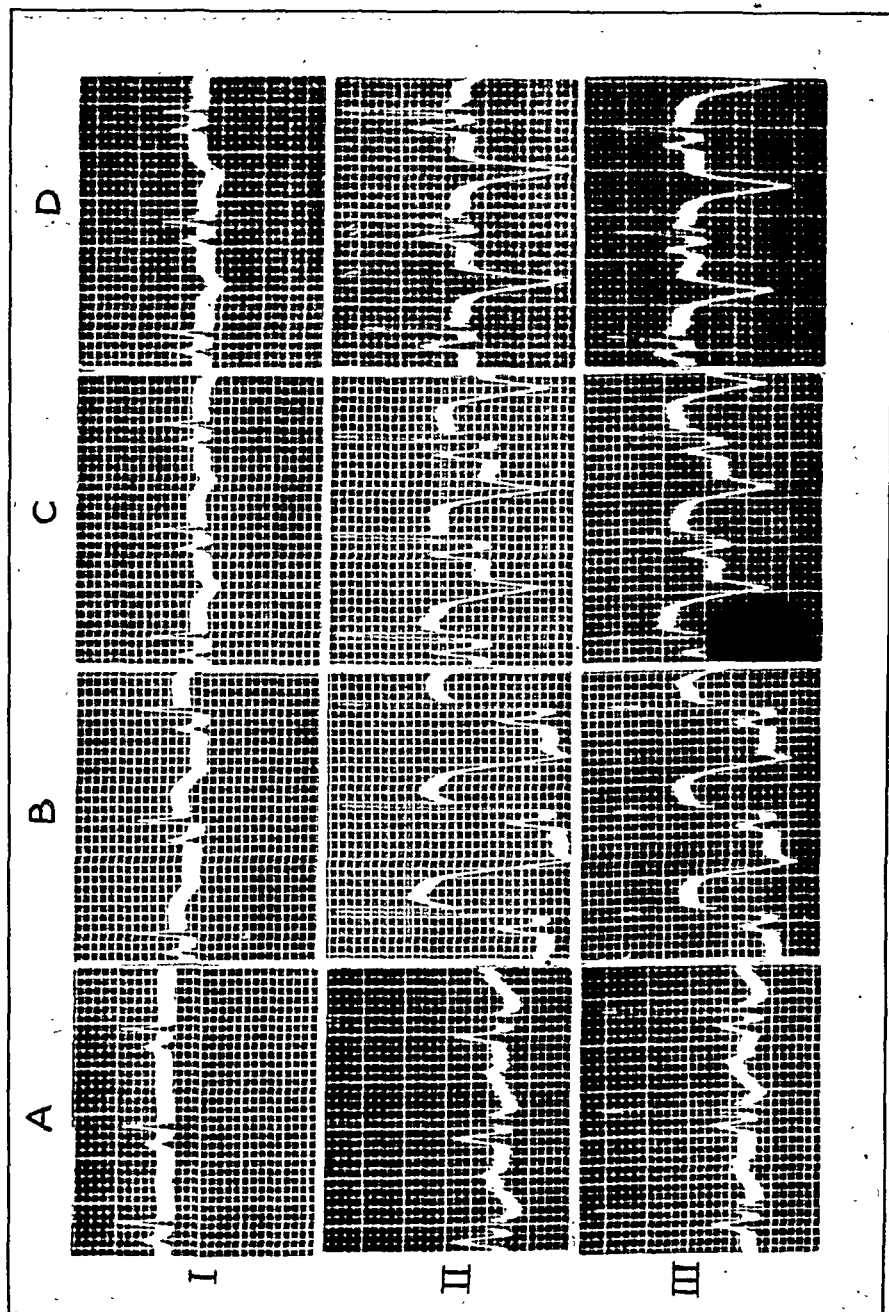


Fig. 3.—Experiment 2. Segment A control before production of myocardial lesion in the apex of the left ventricle anteriorly; Segment B taken 2 min., Segment C, 10 min. and Segment D, 4 hr. after lesion was produced.

Premature systoles and paroxysmal tachycardia followed the production of myocardial lesions in a few instances. These were all, with one exception, ventricular in origin.

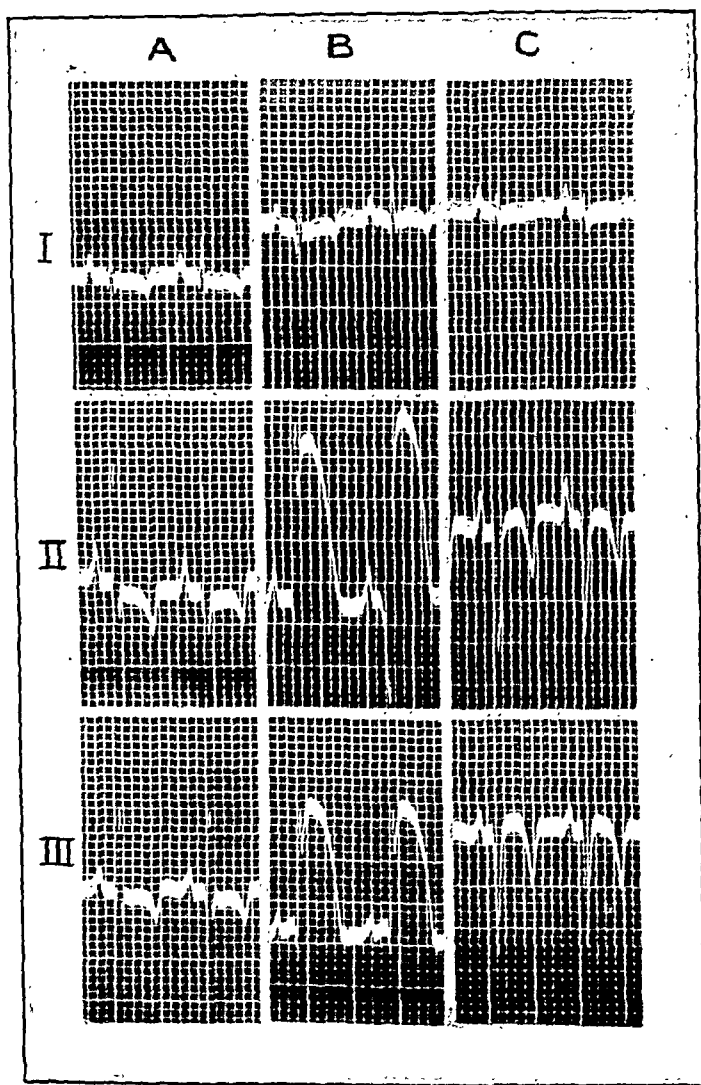


FIG. 4.—Experiment 1. Segment A control before production of myocardial lesion in the apex of the left ventricle anteriorly; Segment B taken 1 min. and Segment C taken 4 hr. after lesion was produced.

It was found that the most striking change occurred in the S-T and T portions of the curve. Practically monophasic curves were seen a number of times soon after production of the lesion (Figs. 3 and 4). Very deep negative and very tall positive coronary T waves (Bohning and Katz¹⁶) were also found (Figs. 5, 6 and 7), the amplitude of which were on occasion as great as ± 25 mm.

When the changes in the *S-T* segment and *T* wave were analyzed, the type of change found did not always fit into the T_1 or T_3 types of Parkinson and Bedford's classification. The changes observed in many instances fell into two additional subdivisions; one group in which the *S-T* segment was at first positive in all three leads, and was later dominated by deep negative coronary *T* waves in all leads; and the other in which the *S-T* segment was at first negative

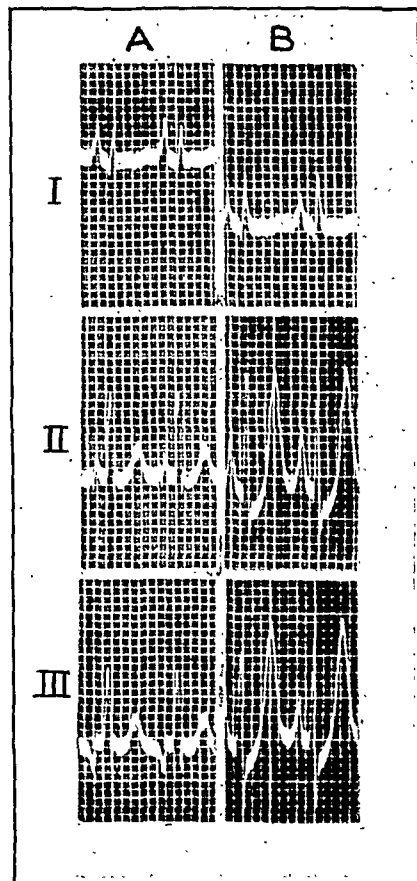


FIG. 5.—Experiment 8. Segment A control before production of myocardial lesion in the middle of the left ventricle anteriorly; Segment B taken 2 hr. after lesion was produced.

in all three leads and was later dominated by tall, upright, coronary *T* waves in all leads. The first of these types we have called the T_n type (Fig. 3) and the latter the T_p type (Fig. 8). In addition to these four types, a number of experiments showed no change at all. In some instances only the early stage, viz., the stage with marked *S-T* deviation or only the latter stage, viz., the stage with marked *T* wave alteration occurred. In some experiments the early *T* type

based on the *S-T* shift was different from the *T* type which appeared later when the *T* wave alterations were at a maximum. Usually it was a T_p type changing to a T_1 type, or a T_n to a T_3 type or *vice versa*. However, we found no instance of a T_1 type changing to a T_3 type or *vice versa*. As a rule the changes in Lead I were not as marked as in Leads II or III. This is understandable since Lead I usually had the smallest complexes to begin with. Furthermore it happened frequently in the T_1 and T_3 types that the *S-T* and *T* changes were absent in Lead I or in Lead III, or that they occurred only in one of these two leads.

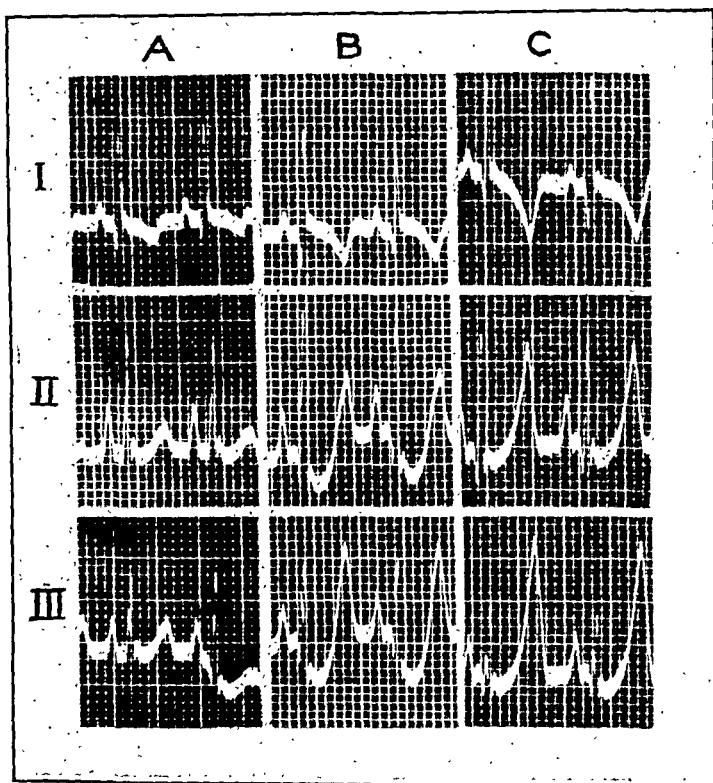


FIG. 6.—Experiment 28. Segment A control before production of myocardial lesion in the base of the right ventricle anteriorly; Segment B was taken 10 min. and Segment C, 2 hr. after lesion was produced.

Inspection of Table 1 shows that it is practically impossible to locate the site of lesion from the *T* type of the electrocardiographic changes. Even though the region were subdivided into relatively small areas the magnitude of change produced by lesions in the same locality was non-predictable. Sometimes a lesion in a given area was accompanied by no electrocardiographic change at all while in other instances a lesion in the same area caused a tremendous shift in the *S-T* segment resulting in a practically monophasic appear-

ance of the ventricular complex, followed later by tremendously inverted or strikingly tall coronary *T* waves. Furthermore, a lesion in one experiment gave a mirror image type of change to that caused by a lesion in the same locality in other experiments (compare

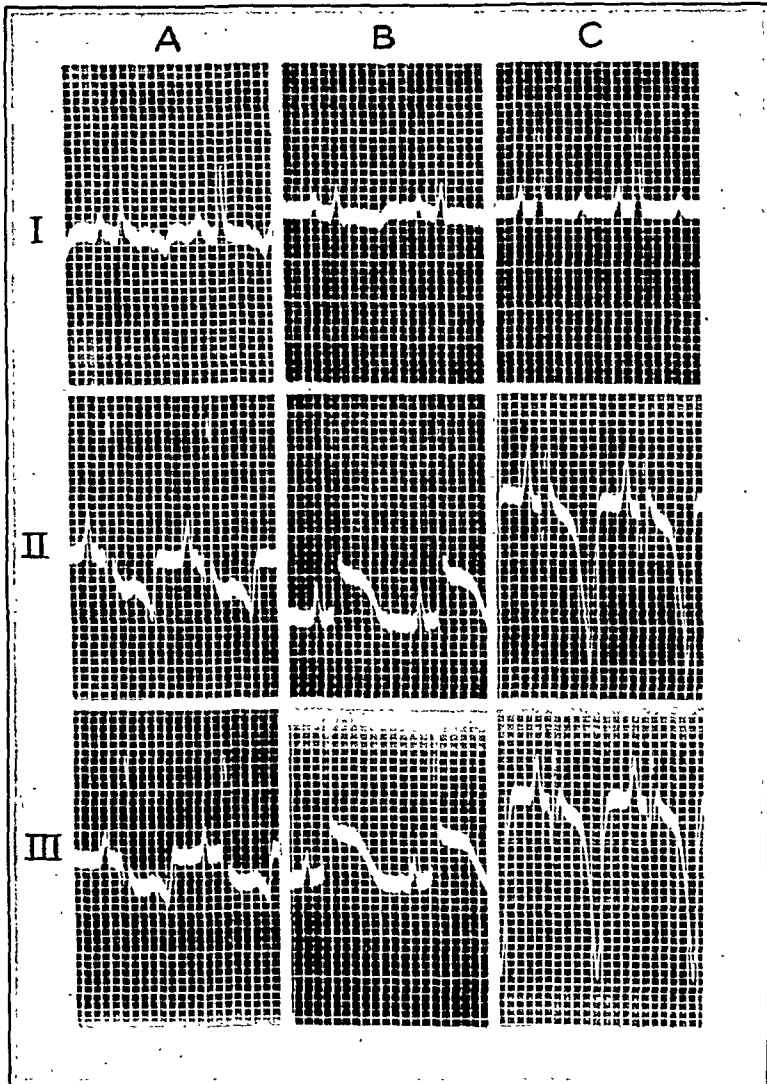


FIG. 7.—Experiment 13. Segment A control before production of myocardial lesion in the apex of the left ventricle posteriorly; Segment B was taken 2 min. and Segment C, 2 hr. after lesion was produced.

experiment 11 with experiments 5 to 10). This variability was apparently not dependent upon the size of the injured area nor upon the position of this area in relation to the epicardium and endocardium.

When an attempt is made to group the 10 small areas used for

injection into larger groups no constant differentiation can be made, as might have been anticipated from the literature, between effects of lesions in the right ventricle and those in the left, or between the effects of lesions located in the anterior wall and those in the posterior, or between effects of lesions in the basal portion of the ventricles and those in the apical portion. Lesions in the septum did not produce any characteristic change which differed from those produced by lesions in the outer walls of the ventricles.

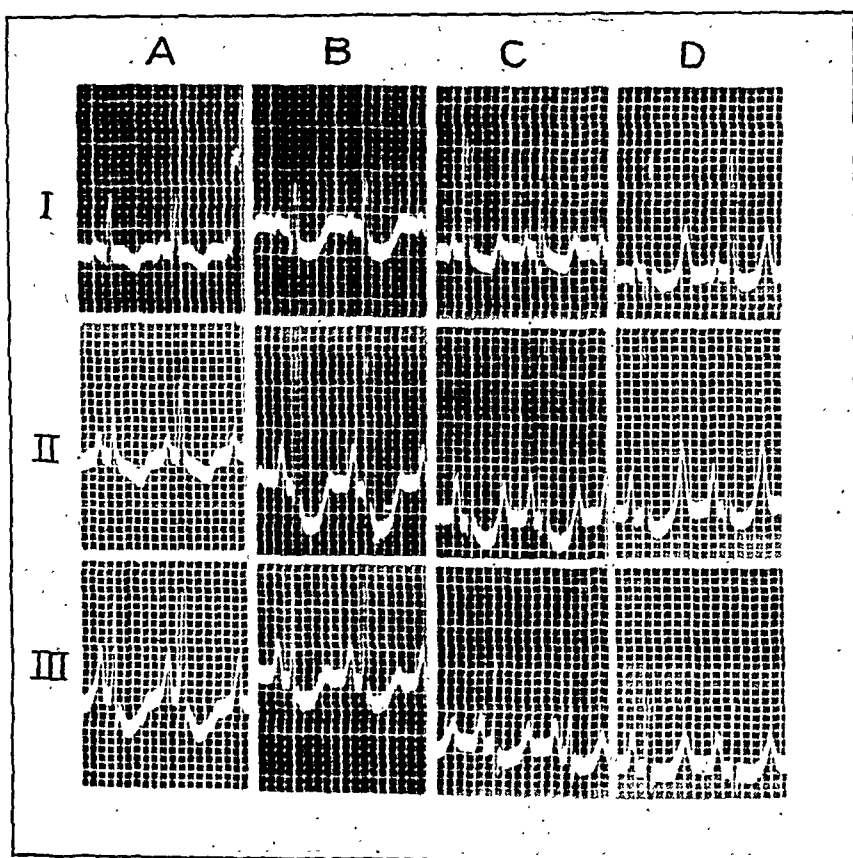


FIG. 8.—Experiment 32. Segment A control before production of myocardial lesion in the base of the right ventricle anteriorly; Segment B was taken 2 min., Segment C, 2 hr., and Segment D, 4 hr. after lesion was produced.

We are compelled to conclude on the basis of this study, either that the location of myocardial injuries is not important in determining the *Q-T* type of electrocardiographic change or at least that factors, as yet unknown, practically mask the influence of the location of the lesions in the heart on the electrocardiogram. While these lesions are not morphologically the same as infarcts and have a different genesis, they nevertheless produce the same type of "injury reaction" in the electrocardiogram. We therefore feel

warranted in applying these results to the "injury reaction" in the electrocardiogram following infarction as far as location of the lesion is concerned. We feel, therefore, that the view that the location of infarctions determines the *Q-T* type of electrocardiographic change does not rest on adequate evidence.

Summary. An analysis was made of the changes produced in the electrocardiogram during the first 4 hr. following injection of 95% alcohol into the dog's ventricular myocardium with the production of sharply demarcated areas of injury. Within a few minutes following injection of alcohol into the myocardium, monophasic ventricular complexes occurred several times. Deep inverted or tall upright peaked *T* waves having rounded shoulders and symmetrical limbs—negative and positive coronary *T* waves—were frequently found later. In addition to the T_1 and T_3 types of curves, two other types of change which we have called the T_p and T_n types occurred frequently. In the T_p type, positive coronary *T* waves occurred in all three leads preceded by negative *S-T* deviations. In the T_n type negative coronary *T* waves appear in all three leads preceded by positive *S-T* deviations.

On subdividing the ventricular myocardium into 10 regions, it was found that the location of the myocardial lesion did not determine the magnitude of the electrocardiographic change nor did it give rise to a characteristic *Q-T* type of change for any locality. It is concluded that using the standard three leads, the electrocardiogram cannot be used to differentiate (1) between injury to the anterior and the posterior wall of the ventricles; (2) between injury to the right and the left ventricle, and (3) between injury to the apical and the basal portion of the ventricles. No constant correlation could be made between the size of the injured area and the magnitude of electrocardiographic change in the standard three leads. The electrocardiographic changes apparently do not depend upon the location of the injured area in relation to the endocardium or epicardium.

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ARTERIOVENOUS FISTULA OF THE RENAL VESSELS.*

BY EDWARD W. HOLLINGSWORTH, M.D.,
CARDIOLOGIST, VETERANS ADMINISTRATION FACILITY,
HINES, ILL.

ARTERIOVENOUS fistula is a not uncommon condition, usually due to trauma, less often congenital, the limbs being the most usual sites. Pemberton¹ states that of 25 cases operated at the Mayo Clinic 16 were acquired. Of several seen at the Veterans Administration Hospital, Hines, Ill., all but 3 were the result of gunshot wounds. The present case is considered of interest because of its unusual location and probable etiology.

Osler,² in speaking of arteriovenous fistula, says: "On palpation the characteristic thrill is felt, vibratory, rough, continuous and increasing with the diastole† of the artery. Except in its roughness it is quite unlike any other thrill felt in cardiovascular lesions and is *pathognomonic*."‡ He later speaks of "the characteristic loud, rough, humming-top murmur, continuous, with marked intensification during the cardiac systole," and also refers to it as "machinery." He gives the important signs as the thrill and murmur, and the dilatation of the veins. Holman³ includes slowing of the pulse, first noted by Branham,⁴ and increase of diastolic blood pressure, upon closing the fistula, as further diagnostic points.

Osler² considered remote effects on the circulatory system rare, although 1 of his patients died of heart failure 31 years after the causative accident. Holman,⁵ discussing its physiologic effects, says that 6 of 21 cases at the Johns Hopkins Hospital showed cardiac enlargement which he believes to be directly due to the fistula. Whether due to increased work, as claimed by Holman,⁵ or deficient coronary circulation, as Lewis and Drury⁶ believe, all observers now agree that cardiac enlargement and eventual failure are common.

Case Report.—M. S., a white male, aged 29, was admitted to the Edward Hines, Jr. Hospital, Hines, Ill., December 3, 1926, for treatment of chronic, active pulmonary tuberculosis. Family history was irrelevant,

* Published with the permission of the Medical Director of the Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the writer.

† Apparently a typographical error, systole being intended.

‡ Italics are author's.

no near relative had tuberculosis. The patient served in the U. S. Army from May to December, 1918. At the time of discharge he felt tired and weak and did not work for 2 or 3 months but then worked steadily until October, 1926. He had renal colic in July, 1925, and was in hospital 1 month, being told that he had a kidney stone. In October tuberculosis of the kidney was diagnosed and removal advised. This was done November, 1926, through the usual lumbar incision, the ureter being removed through the left rectus and the patient was discharged 6 weeks later. For 2 weeks prior to the operation he had a severe cough which gradually subsided.

At the time of admission the wound over the kidney region showed a slight serous discharge and had not entirely healed until the latter part of July. The blood pressure was 110/70 and no abnormal cardiovascular

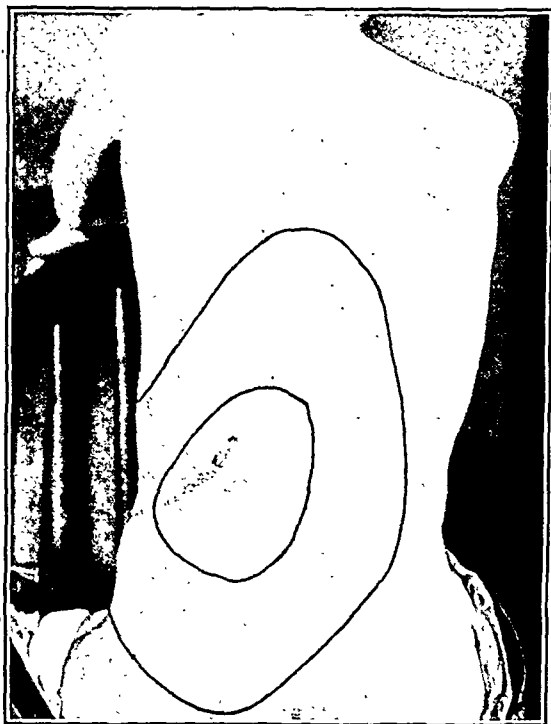


FIG. 1.—Photograph taken June, 1930, showing areas of transmission of thrill (small circle) and bruit (large circle).

findings were noted; chest examination and roentgenogram showed a far advanced pulmonary tuberculosis. January 31, 1928, the patient had pain in the left kidney region, and for a time a septic temperature and rapid pulse, which later became normal, and he was discharged at his own request June 22, 1930, as unimproved.

He was readmitted January 19, 1931, and a psoas abscess found. A body cast was applied and after several months replaced by a corset, with marked relief of symptoms. Genito-urinary examination revealed tuberculosis of the right kidney and bladder. He again had a septic temperature, which gradually fell to normal. The blood Wassermann and Kahn tests were negative, urinalysis and blood counts normal.

The patient was seen by the writer February 27, 1930, his ward surgeon having made a diagnosis of aneurysm. He stated he had first "felt a noise"

over the kidney scar in May or June of 1928 but had no other symptoms referable to the cardiovascular system. Radial pulses were somewhat water-hammer in type, there were no murmurs and no sclerosis of the peripheral arteries. The heart was enlarged to the left, the border being percussed 10 cm. from the midline, impulse forcible. The rate was 90, blood pressure 114/60. A thrill and bruit were present over the nephrectomy scar, the former over a small, the latter over a relatively large, area (Fig. 1). Both were accentuated in systole and were not transmitted down the aorta or its branches and it was found that they could be stopped by bimanual pressure over the back and abdomen* without affecting the pulsations of the aorta, the heart rate falling to 72 and the blood pressure rising to 124/80. The patient experienced no sensation such as Reid⁷ describes. There were no superficial dilated or tortuous veins in the neighborhood.

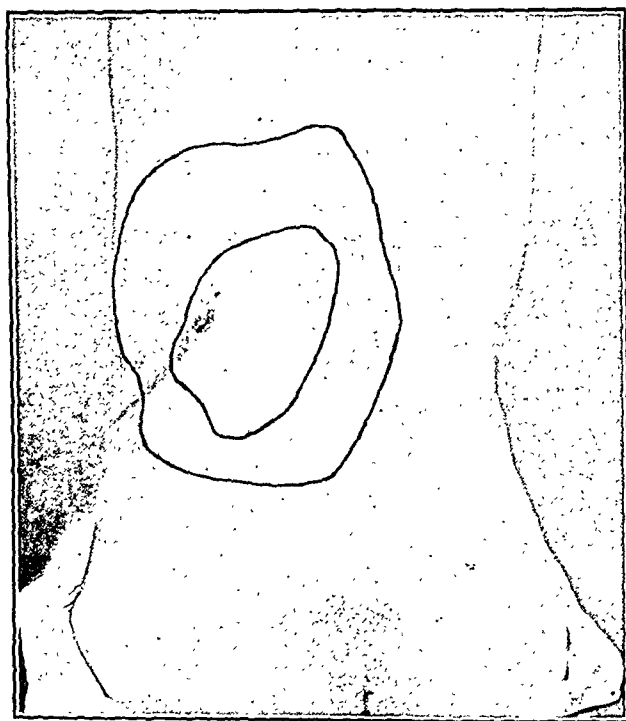


FIG. 2.—Photograph taken July, 1932, showing diminution in areas of transmission of thrill and bruit.

Electrocardiograms were normal on several occasions. Roentgenograms showed an increase of $2\frac{1}{2}$ cm. in the transverse diameter of the heart in less than 3 years although there was roentgenologic and clinical evidence of improvement in the pulmonary tuberculosis. Blood volume^{8,9} was found to be 4916 cc. on December 6, 1931, and 5196 cc. on February 25, 1932, normal for patients' weight of 117. At this time the patient is quite comfortable and his general condition, as well as the psoas abscess and lung tuberculosis, are showing improvement.

Discussion. The question of diagnosis is interesting. The thrill and bruit are indicative of an aneurysm, their intensity and large

* Tracings were taken under similar conditions in 3 other cases—in 2 there was no change in rate, in the third a slight increase.

area of transmission suggest the involvement of large vessels. An arteriovenous one was suggested by the continuous thrill and bruit, "machinery" in type, with systolic intensification, the secondary effects on the general circulation, the characteristic reaction to what was believed to be closure of the fistula, and progressive cardiac enlargement. Because of the location of the thrill and bruit, and known trauma to the renal vessels, it was believed that they were the ones involved; the absence of dilated and tortuous superficial veins indicated the lesion was deep, the absence of aortic thrill and bruit suggested that a branch only was affected and there were no localizing findings pointing to any other intraabdominal vessels.

Arterial aneurysms of the renal artery are generally regarded as rare. Thus, Conroy,¹⁰ in a recent review lists only 32 cases and states that this is one of the rarest, if not the rarest, of all sites. Mathé¹¹ says that they constitute about 1% of all aneurysms and the diagnosis is extremely difficult. Singer¹² reports 2 cases and thinks the condition is much commoner than is generally believed to be the case. So far as could be ascertained but 1 case of arteriovenous aneurysm of the renal vessels has ever been reported.¹³ The patient was a white male aged 27, who when first seen had congestive heart failure, which grew progressively worse until death. There had been no operation, there was no history or evidence of trauma and the diagnosis was made with considerable hesitation but verified at autopsy. Holman¹⁴ states that he knows of no similar case.

The normal blood volume was at variance with the belief of Holman^{3,5} but in accord with results obtained in other cases at this hospital¹⁵ and in the case of Ellis and Weiss.¹⁶ Oxygen content of distal vessels of course could not be determined. No systolic apical murmur was noted. Ophthalmoscopic examination did not disclose any pulsation of the retinal vessels and no definite changes in the size or shape of the heart, described by other authors,^{3,6,16} were found upon closure of the fistula, possibly due to incomplete closure, particularly difficult with the patient in the erect position.

Postoperative infection, trauma at operation and tuberculosis must be considered possible etiological factors. *A-V* communications following the trauma of operation¹⁷ are not rare, there being many cases reported. Tuberculous involvement of large blood-vessels is generally accepted as rare. Baumgarten and Cantor¹⁸ were able to collect but 20 cases of tuberculous aneurysm of medium-sized and large arteries. They mention no case of arteriovenous aneurysm.

Dr. McDougall, staff urologist, investigated the technique employed and states that the renal artery and vein were ligated separately at operation, a procedure calculated to obviate any possibility of such a complication as apparently occurred. The ligatures, however, were passed by means of an aneurysm needle which might account for some additional injury to the vessels. The patient

refuses operation, although this has not been strongly advised, and believes the thrill and bruit are becoming less. By comparing photographs (Figs. 1 and 2) of the areas of transmission, taken some 2 years apart, it would seem that this is so. Spontaneous healing has been noted in small arteriovenous communications experimentally produced,¹⁹ and of course may be taking place in this case. There has apparently been no increase in the cardiac involvement for some time, so the prognosis may be better than originally feared.

Summary. A case is reported in which signs and symptoms suggesting an arteriovenous aneurysm appeared over the site of a nephrectomy scar some 18 months following operation. Progressive enlargement of the heart was noted for a time but the size has now apparently become stationary.

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LARGE DOSES OF TUBERCULIN IN TESTING GUINEA PIGS INOCULATED FOR DIAGNOSTIC PURPOSES.*

By THOMAS B. MAGATH, M.D.,

ASSOCIATE IN SECTION ON CLINICAL PATHOLOGY, THE MAYO CLINIC; ASSOCIATE
PROFESSOR OF CLINICAL BACTERIOLOGY AND PARASITOLOGY, THE MAYO
FOUNDATION, ROCHESTER, MINNESOTA.

THE value of inoculating guinea pigs with clinical material in which *Mycobacterium tuberculosis* cannot be found by direct examination of smears has repeatedly been demonstrated. By this

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biologic test many diagnoses have been made and confirmed when all other laboratory tests have failed.

Since clinical application of the test became general, attempts have been made to shorten the time necessary for diagnosis. If the animals die before 3 weeks after inoculation and tuberculous lesions cannot be found, the test should be considered a failure. Animals should not be killed until at least 8 weeks after inoculation. If spontaneous death occurs between the 3d and 8th weeks, and if lesions of tuberculosis cannot be found, the test should then be reported as negative.

A method advocated by Bloch is to inject the material into the region of the inguinal glands of the animal and then, with the thumb and finger, to traumatize the inguinal lymph nodes gently. This is supposed to cause early involvement of these nodes and thus hasten the diagnosis. Sufficient protocols illustrating the usefulness of this method are lacking, and its advantage is open to question when used with material having other organisms present in it.

Another means of hastening the development of tuberculosis in guinea-pigs by exposing them to a small dose of irradiation with Roentgen rays was amplified by Morton after several investigators had proposed it. The hypothesis in this procedure is that irradiation will reduce the resistance of the animal to such a point that the organisms develop more rapidly. Practically, the dose is so difficult to control and the resistance of the animals varies so much that the method is not suitable for routine use. As a rule, either the animals are killed by an excessive dose or no effect on the outcome of the tuberculous process is obtained.

Occasionally, suggestions have been made that a strain of guinea pigs genetically susceptible to tuberculosis should be developed. Sewell Wright did develop such a strain by inbreeding, but the loss of animals is too great to sustain the strain, and it is not practicable to obtain and maintain such animals.

A technique designed to hasten the development of lesions by direct injection into certain organs, for example, into the liver or eye,⁸ has been proposed. The procedure is useful in certain instances but animals are often killed by it, or die a few days after as a result of hemorrhage or infection. In the long run, the time is not greatly shortened and, on account of this, together with the initial loss, the uncertainty of actually injecting the material into the organ, and the necessary limitation of the amount that can be injected, the method is not recommended as a routine procedure.

An interesting modification of this method has been to inject the material into the mammary glands of an animal with the expectation of recovering the organism in the milk. Obviously this method is lacking in practicability.

Magath and Feldman attempted to hasten the diagnosis by injecting material into the brains of guinea pigs. Two hundred

and eleven specimens were inoculated intracerebrally and the results compared with the routine method. The routine method yielded 31 positive specimens, the intracerebral method only 11. Diagnosis was made in these 11 cases after an average elapsed time of 30 days, whereas the elapsed time in the routine tests was 49 days. Although the intracerebral method did hasten the diagnosis, the number of failures and negative results clearly demonstrated the shortcomings of the method and proved its unsuitableness as a routine procedure.

Murphy and Ellis found that splenectomized mice survived inoculation with bacilli of tuberculosis for a shorter time than controls did, but routine procedure based on this principle is out of the question.

Schulz recommended injecting material intracutaneously, and stated that this would hasten the results. With contaminated material, however, nonspecific abscesses occur, and Schulz himself did not furnish a protocol to substantiate his claims.

Aside from these and other more or less mechanical devices for hastening the development of tuberculosis in these diagnostic animals, investigators have used cutaneous or intracutaneous methods of testing with tuberculin. They have employed doses somewhat comparable to those used in the diagnosis of tuberculosis in man as, for example, 0.1 cc. of a 5% solution. In order to obtain results easiest to read, only white guinea pigs should be used, and the area of injection should be carefully shaved or plucked, or the hair removed by a chemical process, so as not to cause minute abrasions.

The intracutaneous method was devised by Römer, used by Esch and Schürmann, and extensively tested by Graetz. These investigators found that positive reactions often occur in animals 10 to 12 days after inoculation with material containing bacilli of tuberculosis. In applying this method, the rule is to begin testing the animals after 2 weeks, and then to test them every 2 weeks thereafter. Although all of these investigators indicated some errors in their series and others condemned the method on several grounds, consideration of their protocols confirms the conclusion that the test is useful and hastens the positive diagnosis in the majority of cases by from 3 to 5 weeks. Nevertheless, the method requires a careful technique and a considerable amount of time in order to prepare and test the animals. When positive reactions occur at the first test, necropsy must be carefully performed and sectioning frequently resorted to.

The loss of weight has been useful under certain circumstances as an indication that an animal was infected, but if animals are kept in their cages under proper conditions and given good care and food, loss of weight does not become a practical criterion for selecting animals for necropsy before the standard time allotted.

Some years ago Dr. Louis Gross, of Mount Sinai Hospital, New York City, called my attention to a method that he was using. He injected 0.5 cc. of tuberculin subcutaneously into his test animals from 3 to 4 weeks after the original inoculation with the suspected clinical material. In most animals with infection sufficiently advanced by that time, death resulted promptly, and the diagnosis was thus hastened by several weeks. This method was used by Esch and compared with Römer's method; however, the material tested was a pure culture of *Mycobacterium tuberculosis*. Esch concluded that the intracutaneous test was superior.

Experimental Observations. After preliminary tests indicating that normal animals were not killed by so large a dose of tuberculin, it was decided to use the method as a routine in our standard technique as follows: The clinical material was centrifugalized for 1 hour at 2500 r. p. m. in a centrifuge with a head-radius of 13.5 cm. At the end of this time 1 cc. at the top was pipetted off and, after the middle portion had been discarded, this top portion was added to the sediment. The whole was now made up to 5 cc. with physiologic saline solution, and 2 guinea pigs were given injections through the abdominal skin, 1 subcutaneously and 1 intraperitoneally. If a guinea pig died and no gross lesions were evident before 3 weeks had passed, the test was considered a failure; if a guinea pig died and no lesions were present after 3 or more weeks had elapsed, the test was considered negative. If both animals were alive at the end of 4 weeks, the one receiving the intraperitoneal injection was tested by injecting 0.5 cc. of OT tuberculin subcutaneously. If it died and was found to be positive, its mate was sacrificed and examined. All other guinea pigs were permitted to live for 8 weeks and, at the end of that time, were killed and considered either positive or negative depending on whether lesions were present or absent. To anyone experienced in the diagnosis of tuberculosis in such animals, gross lesions can be diagnosed accurately without resorting to histologic examination of tissue. In certain cases, especially when the animal died early, the histologic diagnosis of tuberculosis was used and was based primarily on finding acid-fast bacilli within the lesions. In this series, histologic confirmation of a tentatively positive or negative diagnosis was resorted to 7 times.

In order to compare the advantage of testing with tuberculin, a similar series of animals (400 pairs of guinea pigs or 200 specimens) were injected and studied; the same routine was used but testing with tuberculin was omitted.

Table 1 indicates that the animal injected intraperitoneally is much more likely to become infected than the one injected subcutaneously, but Table 2 reveals the interesting fact that the animal injected intraperitoneally is more likely to die before 3 weeks, thus

resulting in a failure. It occasionally happens that animals injected subcutaneously become positive when their mates are negative,

TABLE 1.—AGREEMENT AND DISAGREEMENT AMONG GUINEA PIGS INJECTED INTRA-PERITONEALLY AND SUBCUTANEOUSLY (400 PAIRS, CONTROL; 400 PAIRS, TUBERCULIN TESTED).

Positive, intraperitoneal*	
Control	10
Tuberculin tested	11
Negative, intraperitoneal†	
Control	2
Tuberculin tested	3
Positive, intraperitoneal‡	
Control	29
Tuberculin tested	58

* Mates negative, subcutaneous.

† Mates positive, subcutaneous.

‡ Mates positive, subcutaneous.

TABLE 2.—DISAGREEMENTS AMONG 400 PAIRS OF CONTROL GUINEA PIGS, DURING THE PERIOD WHEN 400 PAIRS OF TUBERCULIN TESTED GUINEA PIGS WERE INJECTED.

Method of injection.	Result.	Number of specimens.
Subcutaneous	Failure	12
Intraperitoneal	Negative	
Subcutaneous	Negative	42
Intraperitoneal	Failure	
Subcutaneous	Failure	1
Intraperitoneal	Positive	
Subcutaneous	Positive	4
Intraperitoneal	Failure	
Subcutaneous	Failure	12
Intraperitoneal	Failure	

TABLE 3.—COMPARISON OF CONTROL AND TUBERCULIN TESTED GUINEA PIGS, (400 PAIRS, CONTROL; 400 PAIRS, TUBERCULIN TESTED).

	Control.		Tuberculin tested.	
	Number.	Per cent.	Number.	Per cent.
Positive specimens, urine	25	57	39	55
Positive specimens, other material	19	43	33	45
Positive specimens, total	44	11	72	18
Both guinea pig failures	7	1.7	5	1.1
Average elapsed time before diagnosis	53 days		33 days	

TABLE 4.—TUBERCULIN TESTED GUINEA PIGS (400 PAIRS).

Guinea pigs positive and killed by tuberculin	54 (78.3%)
Guinea pigs positive but not killed by tuberculin	15 (21.7%)
Guinea pigs negative but killed (?) by tuberculin*	5
Mate positive	1
Mate negative	4
Guinea pigs negative (not killed by tuberculin); mates positive	2

* These animals died within 48 hours after administering tuberculin, but this number of animals might have been expected to die even if not tested with tuberculin.

and from Table 3 these observations may be strengthened by noting the larger number of positives among the animals injected intraperitoneally when animals injected subcutaneously were failures.

In the series there were a total of 44 positive specimens in the control group and 72 in the tuberculin group (Table 3). In the control group, 7 (1.7 per cent) pairs of animals were failures, whereas during the period when the 400 pairs of tuberculin tested animals were being observed, 5 (1.1 per cent) pairs were failures.

With the exception of 1 or 2 animals that died following administration of tuberculin and had tuberculous lesions, all animals died within 48 hours. This resulted in a positive diagnosis in 54 (78.3%) within 30 days after inoculation. The average length of elapsed time in the whole series was 33 days for a positive diagnosis as compared to an average elapsed time of 53 days in the control series.

Fifteen (21.7%) of the positive animals so tested did not die as a result of the tuberculin, but nevertheless, were found to have tuberculosis when they eventually came to necropsy.

Five animals died within 48 hours after receiving tuberculin, but were negative. This does not necessarily mean that the injection killed them, for approximately this number of animals might have been expected to die from other causes. Of the mates of the 5, 1 was tuberculous. In the series, 2 mates were positive when the tuberculin tested animals were negative and survived the full 8 weeks.

Comment. It is easy to understand why intraperitoneal injections should be fatal more often than subcutaneous injections, since much of the injected material contains pyogenic organisms; but, when injections of equal amounts are made into both animals, just why the animals injected intraperitoneally should more often be positive is not altogether clear.

This balancing of subcutaneously and intraperitoneally injected animals against each other is important and suggests again the desirability of using this procedure as a routine. Similar results were noted previously by Magath and Feldman.

It is apparent that this method of testing with tuberculin will not result in every positive animal being killed promptly, but from the evidence presented more than three-fourths will succumb within 48 hours. Of those not dying as a result of the tuberculin, the chances that any given animal will present evidence of tuberculosis later on is only 1 in 30. A dose of 0.5 cc. of OT tuberculin does not kill a guinea pig that does not have tuberculosis. Hence, the procedure is safe for routine use.

The use of tuberculin by this method clearly results in shortening the time necessary for the animal diagnosis of tuberculosis by about 3 weeks. The length of time compares favorably with that required for diagnosis by cultural methods. That more specimens can be

demonstrated to contain bacilli of tuberculosis by injection of guinea pigs than by cultures has been demonstrated by Magath and Feldman and by others.

In a series reported with material in which organisms could not be demonstrated microscopically, the average length of elapsed time for cultures was 40 days, for guinea pigs 43 days; however, 14 specimens were proved to contain *Mycobacterium tuberculosis* by animal inoculation, whereas only 4 were so demonstrated by cultural methods. In material known to contain organisms by microscopic demonstration, the average elapsed time for diagnosis was 36 days by cultural methods and 46 days by inoculation of guinea pigs. Four specimens yielded no growth on culture, 2 specimens resulted in failures in both guinea pigs, and 1 gave negative results.

The value of the tuberculin test must be weighed against its cost. This will depend to a great extent on the number of animals tested routinely. If tuberculin can be purchased in large quantities, a reasonable price may be obtained. Against this cost must be placed the saving in care and food of these animals for 3 weeks and the advantage of destroying tuberculous animals early. Of course the value to the patient of an earlier diagnosis cannot be placed on a basis of dollars and cents but, actually, the total additional cost of using tuberculin is not great and is far outweighed by its benefits.

Conclusions. When testing clinical material for the presence of *Mycobacterium tuberculosis* by animal inoculation, a pair of guinea pigs should be inoculated, one subcutaneously and the other intraperitoneally. In order to hasten the test, one or both animals should be tested at the end of 4 weeks with 0.5 cc. OT tuberculin injected subcutaneously.

More than three-fourths of the positive animals will be killed within 48 hours and the diagnosis hastened by 3 weeks. The chances that any other given animal will later prove to have lesions of tuberculosis is 1 in 30.

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SO-CALLED "PRIMARY" TUBERCULOSIS OF MUSCLE.

BY HENRY MILCH, M.D., F.A.C.S.,

ASSOCIATE ATTENDING ORTHOPEDIST, HOSPITAL FOR JOINT DISEASES; ADJUNCT
SURGEON, RIVERSIDE HOSPITAL; INSTRUCTOR OF ANATOMY, COLUMBIA
UNIVERSITY MEDICAL SCHOOL,
NEW YORK CITY.

(From the Orthopedic Service of Dr. Harry Finkelstein at the Hospital for Joint Diseases.)

TUBERCULOSIS of muscle, the consequence of a contiguous tuberculous focus, with fistula formation, is not unusual. On the other hand, so-called primary muscular tuberculosis, in the sense of a metastatic, hematogenous infection, secondary to a tuberculous infection elsewhere in the body, is a great rarity. True primary tuberculosis of muscle (*i. e.*, first lesion in muscle) is not known to exist. No less an authority than Virchow doubted the existence of the so-called primary form. However, up to 1932 Hanke¹ noted the record in the literature of about 55 cases of well-authenticated tuberculosis of muscle other than by direct extension. To this must be added the cases described by Ceccarelli² and Prussia.³ In the great majority of the cases the muscles of the extremities were involved. These included the quadriceps, gluteus, palmaris longus, biceps, triceps, flexor and extensor of the finger, abductor pollicis, etc. In the others, the sternomastoid, pectoralis, rectus abdominis and lumbar muscles have been affected (See also Meyerburg⁷). In 1 case, the only one on record, reported by Zahnert,⁴ the tendon itself, of the triceps humeri, was the seat of the tuberculous infection.

We have seen several cases in which the pectoralis major became involved following operation for tuberculous axillary glands. But the following is the first which we have observed, where the tuberculosis appeared to be independent of any contiguous focus.

Case Report. M. S., female, aged 28, was admitted to the hospital in January, 1934, with swelling behind the left knee. The patient has been under observation for many years for a Pott's disease of the spine, with a collapse of the lower dorsal vertebræ. About 10 years ago she developed symptoms in the right knee and a plaster-of-Paris bandage was applied, with resulting stiffness of the knee. One year ago the patient noted pain and enlargement of the left knee, without any apparent cause. There was no malaise and only slight, if any, fever. Motion of the knee was hardly interfered with. About 3 months later a painless, soft swelling appeared behind the left knee joint and she presented herself at the Out-Patient Department. The skin over this mass was not hot or red. Material aspirated from the mass and injected into a guinea pig was reported as being negative for tuberculosis. Since that time the swelling continued to increase in size and the patient began to complain of pain in the anterior portion of the knee, which became definitely enlarged.

On her admission to the hospital on January 15, a large gibbus in the lumbodorsal area, due to a tuberculosis of the spine, was noted. The right knee was subluxated posteriorly and was ankylosed in slight flexion.



FIG. 1.—Photograph of swelling in back of leg.



FIG. 2.—Roentgen photograph of outline of abscess after attempted injection with contrast medium. Note absence of bone involvement.

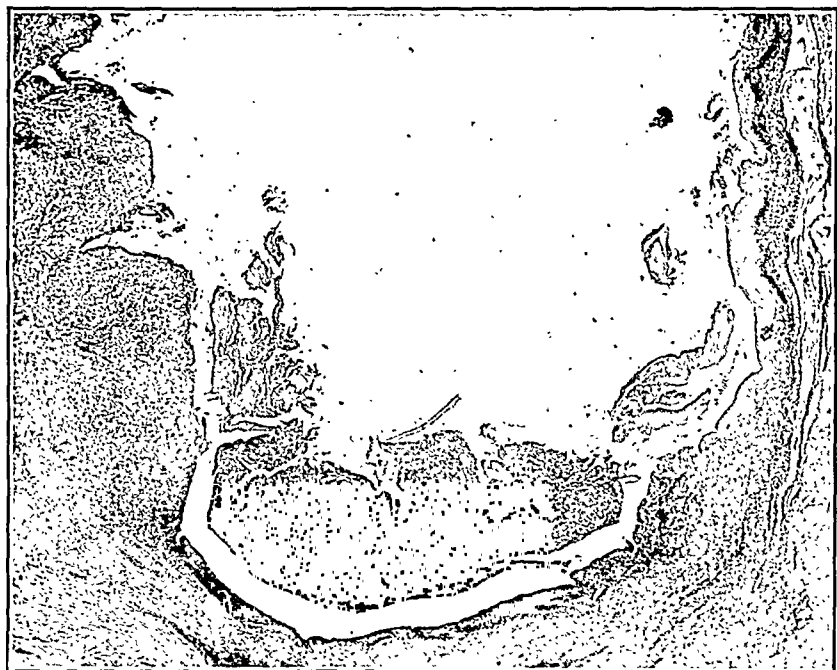


FIG. 3.—Wall of tuberculous abscess cavity in muscle. Note tubercle in upper left-hand corner and portion of caseating mass still present in abscess cavity. ($\times 13$.)

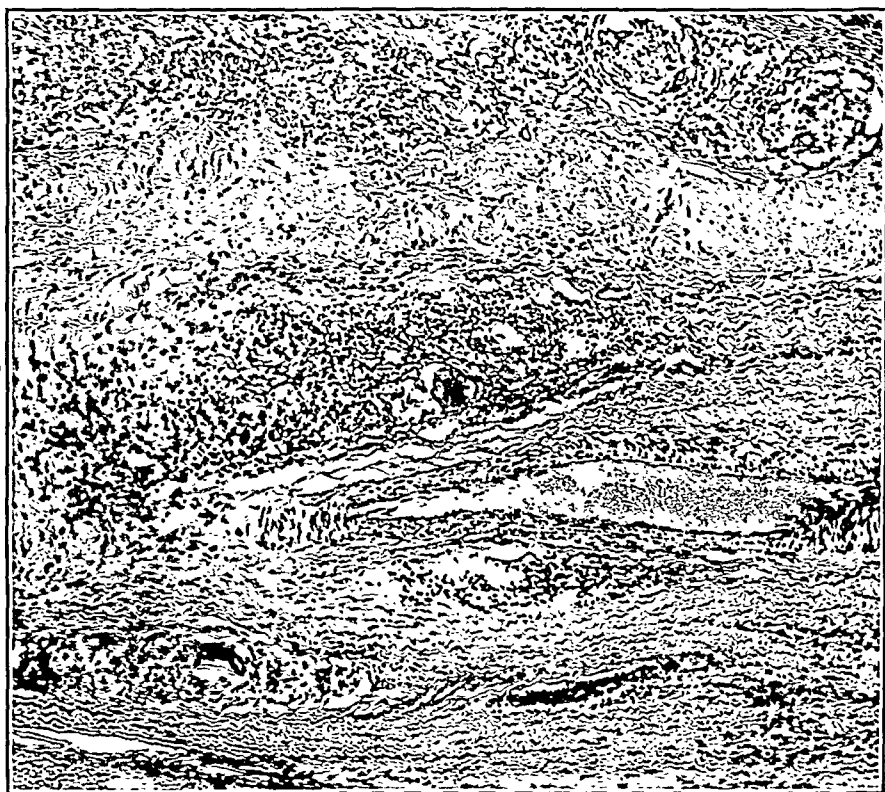


FIG. 4.—Portion of abscess, showing cell exudate with two Langhans giant cells and dense fibrous tissue. ($\times 150$.)

The left knee was definitely enlarged, mainly on its posterior aspect. The tissues about the joint were thickened, but there appeared to be no fluid in the joint. Motion was possible from 180 degree of extension to 120 degrees. There was no abnormal anteroposterior or lateral mobility. On the inner aspect of the left leg, just below the flare of the medial tibial condyle, there was a tense, elliptical, semielastic swelling about 10 cm. in its greatest length (Fig. 1). The skin over this mass was apparently perfectly normal in color, texture and consistency. The mass was not adherent to the skin, but seemed to be fixed to the underlying muscle. On attempting to aspirate this mass, the needle seemed to penetrate into a large cavity, but no fluid could be withdrawn. When the needle was removed, the lumen was found plugged with a gelatinous material. Subsequent examination of this material revealed nothing upon which a diagnosis could be based. Culture was reported sterile. Roentgen ray of the knee was reported by Dr. Pomerantz as showing "the articular surfaces of the femur and tibia to be normal. The joint space is not narrowed and there is no erosion of the articular surfaces of the bones comprising this part. On the posterointernal aspect of the knee a circumscribed, soft tissue mass is visualized within which no calcific deposits can be seen. There is, in addition, distinct distention of the suprapatellar pouch." On the 18th the quantitative tuberculin test was reported as strongly positive. The following week an effort was made to inject the mass with a contrast medium, but this was only partially successful because of the great resistance within the swelling, and stereoscopic roentgenograms were reported as disclosing an "irregularly injected soft tissue mass in the popliteal region the character of which cannot be radiographically determined" (Fig. 2). From these findings a definite diagnosis could not be reached, though it was believed that the condition was either a mucoid tumor or an enlarged bursa.

Operation was performed on January 25 under general anesthesia. When the tissues were exposed, it was found that the mass was entirely localized to the inner head of the gastrocnemius muscle, which was with slight difficulty isolated from its origin on the femur down to its union with the outer half of the muscle. The mass was enveloped by a dense, fibrous capsule, from which a thin layer of muscle fibers arose. During the course of the dissection the sac was accidentally ruptured and a large amount of dry, grayish, granular, caseous material extruded. The irregularly roughened sac occupied the center of the medial head of the gastrocnemius and extended from within about one-half inch of the origin of the muscle to just above its union with the outer head. For the first time, the suspicion of tuberculosis of the muscle arose. There was no connection whatsoever with the joint. In amputating the muscle at its femoral origin, the joint was opened for a distance of about 1 cm., but that portion which could be examined through this small opening appeared to be normal in color and without excess of fluid. The rent was repaired, the wound was swabbed with iodine and closed in layers. Convalescence was uneventful and primary union had occurred by the time the sutures were removed. Subsequently a small fistula developed, but this responded to conservative treatment.

At the present time the condition appears to be completely quiescent. There has been no loss of range of motion in the knee. There is no pain and no evidence of any fluid or other acute symptoms in the anterior compartment of the knee joint, though arthroscopy of the knee performed on February 19 by Dr. Berman, showed a "large mass of fat in villus and in pad formation throughout the knee joint. In many areas this showed the appearance of chronic inflammation. The under surface of the patella showed slight opacity of the cartilage, but no definite erosion could be made out. The internal meniscus was seen in one-half of its extent and seemed normal. It was not possible to see the internal, femoral condyle clearly,

because of the large mass of fat, which obscured it. Several biopsy specimens were taken."

The Pathological Diagnosis: "Tuberculosis of the synovial membrane." The mass of muscle tissue previously removed was reported by Dr. Jaffe, in the following sense:

The gross specimen consists of numerous large pieces of tissue. One of them is very tough and fibrous, being apparently made up of tendon and being in a shape of a sac, the whole measuring 10 cm. in length. The lining is rough and apparently somewhat friable. Another piece is quite irregular in shape and cystic to palpation. It measures 4 cm. in diameter. Upon section it is seen to be a very much softened mass of partly pinkish and partly whitish tissue. Most of the other pieces are extremely friable masses of white tissue, with which a mass of fibrinous exudate is in some areas associated.

Microscopic Examination: Section shows a large quantity of fibrino-purulent material. There is also some living fibrous tissue; although its surface cannot be seen, this is probably synovium. In it are numerous tubercle-like bodies consisting of giant cells, epithelioid cells and lymphocytes. The giant cells appear more like foreign body than like Langhans cells. There are extensive areas of necrosis of the muscle tissue.

Diagnosis. Tuberculosis of the gastrocnemius muscle (Figs. 3 and 4).

The presence of the tuberculosis within the knee joint aroused considerable doubt in the mind of the pathologist as to whether this should be considered a case of primary tuberculosis of the muscle, or whether it was secondary to the contiguous joint involvement. However, the appearance of the specimen at operation, the absence of any fistulous tract connecting with the knee joint, the fact that the proximal portion of the medial head of the gastrocnemius, for about $\frac{1}{2}$ inch beyond its insertion into the femur was grossly completely free of any tuberculous involvement, and the complete localization of the abscess cavity within the inner half of the gastrocnemius, would seem to justify the feeling that this is truly a case of involvement of the gastrocnemius muscle, independent of the tuberculous affection of the knee joint proper.

Though not commonly known, the clinical features of tuberculosis of muscle have been so well delineated by Bandelier and Roepke,⁵ and later in greater detail by Zahnert (*loc. cit.*) that a brief recapitulation of their work may be condoned. All authors have been considerably exercised to account for the great infrequency of primary infection of muscle. Some have thought that this was due to the fact that tuberculosis is not prone to affect this highly differentiated tissue; others have believed that the reason lay in the relatively good circulation usually present in muscle. Still others have explained it as due to the presence of the normal muscle juices and the accumulation of lactic acid after function.

Muscular tuberculosis may occur at any age, but appears to be more common during the ages of 17 and 24. Males are more frequently affected than females. As noted above, the muscles of the extremities are more often involved than the muscles of the trunk. Injuries and excessive use, such as might be expected in men engaged in work, seem to predispose to the development of the condition.

Pathologically, the disease may be either of the typical giant-cell forming or of the endothelioid cell varieties. The vascular intima is for the most part the site of the localization of the tubercle bacillus. The interstitial connective tissue is first affected and the muscle tissue is only secondarily involved. Three main types have been described: 1, The tuberculous nodule; 2, the cold abscess; 3, the sclerosing interstitial myositis. To these have been added two other subdivisions; the fungus type and a pseudoneoplastic type observed in the abdominal muscles and corresponding in the main with a similar type of luetic infection elsewhere described.⁶

Clinically, the disease is extremely insidious and may remain unnoticed for a long time. Pain and fever are seldom seen. The general condition remains unaffected and attention is generally attracted to the condition by the appearance of a gradually enlarging swelling, which slowly becomes elongated in the direction of the muscle fibers. It is situated beneath the deep fascia and the skin over it is freely movable. As in other muscle tumors, the mass can be moved across the direction of the muscle fibers, when the muscle is relaxed, but becomes fixed upon contraction. The process is usually well encapsulated and seldom involves the surrounding structures, though different muscles may be involved at the same time. Because of its deep situation, the skin over the mass is never perforated and retains its normal color and texture.

The appearance of a normal skin overlying a definite tumor of muscle in a patient already afflicted with tuberculosis must arouse the suspicion of tuberculosis of the muscle. Differentiation must, of course, be made between this condition and the other types of muscle tumor occasioned by true neoplasms, parasitic disease, teratomata and inflammations, either of the acute, pyogenic type, or that due to the chronic granulomatous infections.

In the sense that tuberculosis of muscle is not known to lead to generalized tuberculous infection, the prognosis is good. On the other hand, spontaneous cure has never been observed. The treatment of choice is by excision of the affected muscle. Incision and curettage of the lesion has been advised, but is not to be recommended. Where the location of the disease is such that excision is impossible, the use of Bier's hyperemia, aspiration and injection of the cavity by means of 10% iodoform in glycerin, and Roentgen ray therapy have been used with satisfactory results. As in all forms of tuberculosis, the general care of the patient is a matter of prime moment.

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BOOK REVIEWS AND NOTICES.

SPINAL ANESTHESIA. Technic and Clinical Application. By GEORGE R. VEHR, M.D., Salem, Oregon. Pp. 269; 81 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, \$5.50.

THE author states that this work, dedicated to the late J. C. Da Costa, constitutes a survey of the experimental and clinical records in the field of spinal anesthesia for the past 49 years. The style in this monograph is not an easy one, many of the chapters having been written in a choppy manner. In numerous instances the historical data are not correct. The author states "light and heavy novocain fluids, long used by Babcock" when it is well known that Babcock used stovain for many years. Ferguson is repeatedly spelt Furguson. In numerous other particulars the work falls short of the Reviewer's anticipations. Statements such as "the blood sugar immediately began to pyramid, with the greatest velocity in the first eight to ten hours" after ether anesthesia can hardly be true, since anyone who is at all familiar with the subject well knows that, although there is a marked rise in the blood sugar immediately after ether anesthesia is begun, there is a fall to nearly normal within a short time after recovery from the anesthetic. The work of Austin and his coworkers shows that acidosis is not a serious factor, as is here stated, in ordinary ether anesthesia. Nor is the statement that "in ether anesthesia, the poisons are generated by the destructive metabolic processes which limit the ability of body cells to utilize the blood sugar," a clear statement of the metabolic changes that occur in ether anesthesia. Spinal anesthesia needs no defense that is based on misstatements of the effects of other anesthetics, and the author's monograph would have been greatly improved had he avoided such pitfalls. The illustrations are excellent, and much of the practical discussion is interesting and valuable. In too many instances the author has, however, included clinical data which add little to the work and in some instances even show a failure critically to evaluate scientific material. For those who desire a reference book on spinal anesthesia this book will fill a need. The author states justly that "the greatest safety to the life of the patient in spinal anesthesia lies in specialization in technic by surgeons under experienced tutors. When dealing with human lives there is little room for the unexperienced." I. R.

ACUTE INTESTINAL OBSTRUCTION. By MONROE A. McIVER, M.D., Surgeon-in-Chief, Mary Imogene Bassett Hospital, Cooperstown, N. Y. Pp. 430; 62 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, \$7.50.

THIS excellent monograph is divided into three major divisions: Part I, giving a general picture of the disease; Part II, dealing with diagnosis and treatment; and Part III, covering experimental work. There are in all 34 chapters, each followed by an excellent bibliography. The illustrations are good. The style is so smooth and the text so interesting that the Reviewer found himself reading it as he would an interesting novel. The author has thoroughly covered the historical aspects of each topic which he reviews. His clinical deductions are sound and the experimental aspects of intestinal obstruction are reviewed in a brilliant manner. He has been most modest of his own contributions to this very important field.

He has carefully covered the high and low obstructions and the common and uncommon causes of obstructions. He has in an unbiased manner carefully weighed the evidence as to the cause of death in the various types of lesions and has evolved from the best available sources the most rational methods of treatment. He has sanely evaluated the experimental investigations into this subject and has shown that much of this work can be directly applied to clinical practice. But the Reviewer must not say too much, for there is not a surgeon who can afford to be without this volume.

I. R.

SURGERY OF A GENERAL PRACTICE. By ARTHUR E. HERTZLER, M.D., Chief Surgeon, Halstead Hospital; Professor of Surgery, University of Kansas, and VICTOR E. CHESKY, M.D., Chief Resident Surgeon, Halstead Hospital. Pp. 602; 472 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, \$10.

THE basis of this book is the last edition of the senior author's *Minor Surgery* (1930), but the work is so completely rewritten that its origin could hardly be recognized. The three parts deal with "Special Surgery," "Regional Surgery" and "General Surgical Considerations." In all there are 31 chapters, well illustrated and, to a large extent, written in the inimitable Hertzler style. It may be questioned whether many of the subjects covered belong in a textbook covering the surgery of a general practice, but one can hardly say what is and what is not "minor surgery." The authors state that "those who shy at state medicine may serve the cause best by serving the patient efficiently, inexpensively and quickly. When the general practitioner cared for the ailing public, there was no complaint about the high cost of hospital care." This book will rapidly find its way into many bookshelves which already contain numerous volumes on similar subjects. It justly deserves this recognition.

I. R.

MODERN DRUG ENCYCLOPEDIA AND THERAPEUTIC GUIDE. By JACOB GUTMAN, M.D., PHAR.D., F.A.C.P., Consulting Physician, Manhattan General Hospital, etc. Pp. 1393. New York: Paul B. Hoeber, Inc., 1934. Price, \$7.50.

THIS tremendous book attempts to bring within one cover details of 8160 "popular" drugs of known and unknown composition, together with therapeutic information (396 pages) from three points of view: (1) Preparations classified chemically and pharmacologically; (2) preparations used in 16 specialties; and (3) diseases and the preparations indicated in their treatment.

Suffering from the unavoidable handicaps of such an approach, this book, like others of its type, betrays its limitations, even its traps, when one tries its use in a familiar field. As an up-to-date source of considerable information presented "without bias or comment," it has a distinct field of usefulness; it should not be used (and perhaps was not so intended) as a guide in the treatment of disease. A 60-page bibliography is a notably useful feature which makes its various parts readily usable.

E. K.

COCCIDIA AND COCCIDIOSIS OF DOMESTICATED, GAME AND LABORATORY ANIMALS AND OF MAN. Monograph No. 2, Division of Industrial Science, Iowa State College. By ELERY R. BECKER, D.Sc., Associate Professor of Protozoölogy, Iowa State College. Pp. 147; 25 illustrations. Ames, Iowa: Collegiate Press, Inc., 1934. Price, \$2.50.

APPRECIATION of the economic importance of coccidiosis as a disease of domestic, game and laboratory animals is mainly the result of investigations

completed within the past few years. This monograph is a timely analysis of published material. The first chapter gives a general account of coccidia and coccidiosis. The next 22 chapters (all very brief) contain discussions of the disease in various animal hosts. An appendix of three sections gives references to species not mentioned in the text, a host catalogue and notes on technique. There is also an extensive bibliography. Authors and subjects are indexed separately. Those who are directly or indirectly interested in coccidia or in animals parasitized by them should find this book helpful.

H. R.

TREATMENT IN GENERAL PRACTICE. By HARRY BECKMAN, M.D., Professor of Pharmacology at Marquette University School of Medicine, Milwaukee. Pp. 889. Second edition, revised and entirely reset. Philadelphia: W. B. Saunders Company, 1934. Price, \$10.

THOROUGH revision, the inclusion of some new material, the deletion of some of the old—in all of which the author shows an increasing and sound conservatism—combine to make the new edition an even better book than the first and highly to be recommended to all physicians.

R. K.

TREATMENT OF THE COMMONER DISEASES. By LEWELLYS F. BARKER, M.D., Professor Emeritus of Medicine, Johns Hopkins University; Visiting Physician, Johns Hopkins Hospital, Baltimore. Pp. 319. Philadelphia: J. B. Lippincott Company, 1934. Price, \$3.

BASED upon ten post-graduate lectures to the Academy of Medicine of Lima and Allen Counties, Ohio, this volume deals "with the management of some of the internal disorders that are not infrequently met with by the physician who engages in general practice." The author states "I shall make no attempt to discuss fully and completely any topic whatever; but I shall feel free to wander whither I will, making running comments upon any subject that may occur to me as being pertinent to general medical practice." The author's rich experience, sound judgment and delightful style combine to make this little book valuable "brush-up" reading for the busy practitioner. A further feature is the large number of references (over 600) to original sources. The Reviewer, however, permits himself to differ with the recommendation to give quinine intravenously to patients who have an idiosyncrasy to quinine by mouth, as well as with that to use vigorous salvarsan treatment in syphilis of the liver.

R. K.

NEW BOOKS.

The Surgical Clinics of North America, Volume 14, No. 3 (Mayo Clinic Number—June, 1934). Pp. 221; 70 illustrations. Philadelphia: W. B. Saunders Company, 1934.

Collens System of Diet Writing. Including Diet Calculator, Obesity Chart, 100 Menu Prescription Forms. By WILLIAM S. COLLENS, B.S., M.D., Chief, Diabetic Clinic, Israel Zion Hospital; Assistant Physician, Greenpoint Hospital; Metabolist, Brooklyn Women's Hospital; Consulting Metabolist, Rockaway Beach Hospital. New York: Form Publishing Company, 1934. Price, \$5.

German Medicine. By W. HABERLING, M.D., Professor of The History of Medicine, Academy of Düsseldorf. Translated by JULES FREUND, M.D., Ex-Associate in Bacteriology, University of Pennsylvania. Vol. 13 of *Clio Medica*. Pp. 160; 9 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, \$1.50.

- Medicine in Persia.* By CYRIL ELGOOD, M.D., M.R.C.P., Late Physician to the British Legation, Teheran, Persia. Vol. 14 of *Clio Medica*. Pp. 105; 11 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, \$1.50.
- Lane Medical Lectures: Biochemical Studies of Nutritional Problems.* Vol. 3, No. 2 of Stanford University Publications. By J. C. DRUMMOND, Professor of Biochemistry, University College, University of London. Pp. 106; 6 figures. Stanford University, California: Stanford University Press, 1934. Price not given.
- The Spastic Child.* A Record of Successfully Achieved Muscle Control in Little's Disease. By MARGUERITE K. FISCHER. Pp. 97; 2 illustrations and 14 figures. St. Louis: The C. V. Mosby Company, 1934. Price, \$1.50.
- The Laboratory Notebook Method in Teaching Physical Diagnosis and Clinical History Recording.* By LOGAN CLENDENNING, M.D., Professor of Clinical Medicine in the University of Kansas. Pp. 71. St. Louis: The C. V. Mosby Company, 1934. Price, 50¢.
- Médecine et Éducation.* By G. MOURIQUAND, M. PÉHU, P. BERTOYE, J. BARBIER, P. VIGNARD, P. MAZEL, ABBÉ MONCHANIN, R. P. CHARMOT, and P. D'ESPINEY. Groupe Lyonnais d'Études Médicales, Philosophiques et Biologiques. Pp. 234; 1 illustration. Lyon: P. Lavandier, n.d. Price, 12 fr.
- Craniocerebrale Schemata für die roentgenographische Lokalisation.* By PROFESSOR DR. A. SCHÜLLER, Consiliarius am Zentral-Roentgen-Institut des allg. Krankenhauses in Wien (Leiter Dozent E. C. MAYER), and DR. H. URBAN, Assistent der psychiatrisch-neurologischen Universitätsklinik in Wien (Vorstand Prof. Dr. O. PÖTZL). Pp. 8; 17 illustrations and 1 cellophane sheet. Leipzig: Franz Deuticke, 1934. Price, M. 4.
- Die Ophthalmologie des Suśruta.* Textkritisch bearbeitet, übersetzt und mit Concordanztabellen zu Bhāvamiśra versehen. By DR. MED. ET PHIL. A. ALBERT M. ESSER, Augenarzt in Düsseldorf. Heft 22 of *Studien zur Geschichte der Medizin*. Pp. 83. Leipzig: Ambrosius Barth, 1934. Price, Rm. 7.50.

NEW EDITIONS.

- An Introduction to Practical Bacteriology. A Guide to Bacteriological Laboratory Work.* By T. J. MACKIE, M.D., D.P.H., Professor of Bacteriology, University of Edinburgh, etc., and J. E. MCCARTNEY, M.D., D.Sc., Director of Research and Pathological Services, London County Council, etc. Pp. 504. Fourth edition. Baltimore: William Wood & Co., 1934. Price, \$4.
- Manual of the Diseases of the Eye.* By CHARLES H. MAY, M.D., Director and Attending Surgeon, Eye Service, Bellevue Hospital, New York, 1916 to 1926; Consulting Ophthalmologist to the Mt. Sinai Hospital, to Bellevue Hospital, to the French Hospital, New York, and to the Monmouth Memorial Hospital, etc. Pp. 496; 376 illustrations including 25 plates with 78 colored figures. Fourteenth edition, revised. Baltimore: William Wood & Co., 1934. Price, \$4.
- This manual for students and practitioners continues its successful course.
- Applied Physiology.* By SAMSON WRIGHT. Pp. 604; 195 illustrations and 1 colored plate. Fifth edition. New York: Oxford University Press, 1934. Price not given.

PROGRESS OF MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., CM.,

PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY OF TORONTO,
TORONTO, CANADA.

THE PATHOLOGY OF PNEUMONOCOONIOSIS: A REVIEW.

SIXTY-SEVEN years ago Prof. Kussmaul, of Freiburg in Breisgau, wrote: "The inhalation of dust particles as a disease-producing potentiality has, with good cause, greatly occupied the medical profession in the last two hundred years, as witness of which there is to be found a large series of excellent treatises by English, French, German and Belgian physicians, dealing with diseases of labouring classes whose occupations compel them to work in dusty air." If, in Kussmaul's time, there was already a large series of treatises on the subject, how may the present-day mass of literature be represented?

The many contributions of recent years have attacked the problem from various angles, and none with greater effect perhaps than those which have dealt with the pathogenesis of the disease; for upon an elucidation of the underlying morbid process awaits the hope of therapy and prevention. It is in consequence of a current tendency to question some of the older conceptions of the pathology of dust diseases that the need for a review arises.

Though, broadly speaking, all occupations involving habitual exposure to dusty atmospheres have been attended by some menace to health, attention has been gradually focused more acutely on those industries in which the workers suffer from a high incidence of pulmonary phthisis; and the more offensive dusts have been gradually singled out, until of late years the incriminating finger of scientific scrutiny points almost exclusively to one common constituent of the earth's crust, namely, silica, as the chief if not the only source of the phthisis-producing dust of industry.

The evidence against silica is based largely upon studies of vital statistics, such as have been made by Collis (1915, 1919, 1921, 1933), Middleton (1919), Greenburg (1925), Stewart (1929), Russell (1930), Policard and Martin (1930), and the credibility of the evidence rests upon the demonstration that uncombined silica (SiO_2) comprises or is a constituent of nearly every dust concerning which vital statistics display a high death rate from phthisis among the affected peoples.

Of late, however, doubt has arisen in several quarters as to the accuracy of attaching all the blame to silica. It has been seriously

questioned whether some other mineral substances may not also give rise to dangerous dusts in industry; whether, in fact, the disease entity which has come to be more or less universally recognized as silicosis may not be due, in some instances at least, to the inhalation of dusts which contain no uncombined silica. With the idea, therefore, of seeking to avoid misapplication of the term silicosis to disease processes possibly not caused by silica, the more comprehensive term pneumoconiosis (coined by Zenker, in 1866, meaning literally "lung full of dust") will be used wherever possible in this review.

It will not be amiss to summarize briefly the tissue changes which characterize pneumoconiosis. These have been well described by numerous authorities. (Greenhow, 1865, 1866, 1867, 1869; Zenker, 1866; Arnold, 1885; Ziegler, 1908; Shattock, 1914; Watkins-Pitchford, 1914, 1915, 1927; Watt, Irvine, Johnson and Stewart, 1916; Middleton, 1919; Landis, 1919; Mavrogordato, 1922, 1926; Kettle, 1925, 1933; Cummins, 1927, 1931; Ickert, 1928; Schridde, 1929; Gardner, 1929; Strachan, 1930; Simson, 1930; Strachan and Simson, 1930; Irvine, Simson and Strachan, 1930; Giese, 1931; and Leporin, 1931.) Up to a certain point, all the common inorganic dusts, when inhaled in appreciable quantities over long periods, produce remarkably similar effects upon the lungs.

The Phases of Pneumoconiosis. The initial insult is felt by the lining membranes of the air passages. Collis (1915), who has dealt fully with this phase of the reaction, asserts: "Bronchitis is, *par excellence*, the chief of the pneumoconioses"; and Strachan and Simson emphasize the presence of a dry bronchiolitis from the start. Nearly all authors stress the persistence of a bronchitis throughout the course of the disease; and, save to mention that it varies in severity from one type of dust to another, it need not occupy our attention further.

Gardner (1933) describes 5 phases of the reaction, which, with slight modifications to fit the terminology of other writers and combining his 3rd and 4th phases under one heading, will serve as a basis upon which to summarize the main reactions.

1. *Early Parenchymatous Lesions.* When appreciable quantities of dust first permeate the air sacs many phagocytes wander out from the alveolar walls to ingest the particles and a state of catarrhal inflammation is set up. If the dust be particularly irritant or accompanied by pathogenic organisms, a sharp inflammatory process in the form of a bronchopneumonia may supervene. This is commonly what happens in experimental animals during dusting experiments, and with them the pneumonia often proves fatal. If they survive such an attack, patches of the pneumonia commonly fail to resolve, and plugs of exudate containing many dust-laden phagocytes undergo organization and form balls of cellular fibrous tissue within alveolar ducts and atria. Such lesions have often been misinterpreted as constituting "silicotic nodules," an error which vitiates some of the experimental work to be considered later. In the absence of pneumonia, or following its subsidence, the lung attempts to rid itself of dust-laden cells within the air sacs. Phagocytes which are grossly overloaded with foreign particles, and having little ameboid activity, are slowly evacuated into the bronchioles, carried up by the ciliary action of the bronchial mucosa and finally expectorated. More active phagocytes penetrate the alveolar walls and gain access to the lymphatic channels within the interstitial framework of the lungs.

2. *Lymphatic Stasis.* At this stage pneumoconiosis becomes essentially a disease of the pulmonary lymphatic system, a chronic, obstructive lymphangitis of the lungs. In order to grasp the significance of this condition it is necessary to understand the anatomy and function of the pulmonary lymphatic drainage as described by Arnold (1880), Miller (1911), Haythorn (1913) and Simson (1930). Briefly, the lymphatic system of the lung consists of a series of irregular and ill-defined channels in the subpleural and interlobular connective tissues and in the adventitial coats of bloodvessels and bronchi; these channels are equipped with rudimentary valves (Dunham, quoted by Landis, 1919); they converge at the hilus and drain into the tracheobronchial glands. A sharp distinction should be made between lymphatic channels and lymphoid tissue; the latter constitutes lymph nodes which act as traps or filters along the course of the channels. Small lymph nodes are present in the pleura and along the bronchi, becoming larger and more numerous toward the hilus, where they merge with the tracheobronchial and mediastinal glands. To the pulmonary lymphatics belongs the important function of providing an exit from the lung for phagocytes laden with foreign particles or microorganisms, and they also serve a significant purpose in the resolution of inflammatory processes (Haythorn, 1913).

As dust is evacuated from the lung *via* the lymphatic route it piles up in the nodes, which soon become congested to such a degree that they develop a diffuse hyperplasia of their reticular cells amounting to a fibrosis, in which the dust particles are more or less permanently incarcerated (Herring and McNaughton, 1922). Then stasis develops in the afferent lymphatic channels and gradually spreads farther and farther afield, until the lung is streaked and mottled with dust collections. This is not necessarily a permanent state of affairs (Haynes, 1926). Given rest from further exposure, much of the dust in the afferent channels may be removed (Mavrogordato, 1926), or if edema supervenes, the dust-laden phagocytes may be reactivated and migrate bilusward or backward into the air sacs again (Haythorn, 1913). In the event of continued inhalation the lymphatic channels eventually become congested and choked with dust-laden phagocytes. The phagocytes tend to break down and the liberated particles are transferred to reticular cells, which increase in number and give rise to a moderate permanent thickening of the connective tissues in the pleura, interlobular septa and adventitial coats of bloodvessels and bronchi. When examined microscopically, sections from such a lung show the bloodvessels and, to a lesser extent, the bronchi and bronchioles (Haynes, 1926) mantled with a coat of dust-laden reticular cells, often enclosing small channels filled with dust-laden phagocytes, collections of which Mavrogordato likens to thrombi. Similar deposits of pigment may be seen immediately under the pleura and in the interlobular partitions, but not in the alveolar walls (Simson, 1930). The vessels are not affected by the surrounding dust and fibrosis. One or two authors have described an endarteritis obliterans in relation to pneumoconiosis, but others have shown that it does not occur. With most inert foreign materials, the commonest example of which is coal dust, this is the sum total of the reaction. Landis (1919) points out that lymphatic pneumoconiosis of mild degree is present to some extent in nearly all adult city dwellers, but rarely interferes with health. Mavrogordato

(1926) observes that the pulmonary lymphatics may be occupied for years, even by a so-called phthisis-producing dust, without provoking clinical signs or appreciable fibrosis.

3. *Perilymphatic Fibrosis and Beading.* With the more injurious dusts additional changes commonly take place. The interstitial tissues with which the dust is in contact begin to thicken and nodular aggregations occur at the points of junction of various lymph channels where small receptacula are formed, particularly where the interlobular septa join the pleura and where the bronchi and bloodvessels bifurcate. These aggregations constitute the "pseudotubercles" of Mavrogordato (1922) and the "intralymphatic plaques" of Carleton (1924) and the "beading" commonly referred to by roentgenologists. Mavrogordato observes "the pigment-bearing cells accumulate at certain points (along the lymphatics), bringing to mind 'log jams' at the turns and shallows in rivers of a lumber country." Groups of dust-laden cells collect in these plaques and lay down a fine network of reticular fibrils (Gardner, 1932), thus giving rise to a permanent lesion (Carleton, 1924), which, however, does not yet constitute the so-called "silicotic nodule" to be considered presently. Mavrogordato (1922) has suggested the term "lymphatic cirrhosis" of the lung as applicable to this phase of pneumoconiosis. It should be emphasized that up to, and including this stage, the parenchyma of the lung is as yet uninvolved by any permanent change. Though beading of the linear lymphatics is regarded as positive evidence of a pneumoconiosis from the standpoint of compensation, the discrete, parenchymal nodules, held to be specific for silicosis, are as yet lacking.

The gross appearances of the lung at this stage of pneumoconiosis are characterized by excessive pigmentation, for, whatever be the essential nature of foreign particulate matter within the lung, it is always of a mixed character and contains colored matter in the form of carbonaceous or argillaceous particles or both. Pigmentary injection of the pulmonary lymphatics shows itself then to the naked eye as marbling of the pleura, streaking and mottling of the cut lung surface and uniformly deep coloring of the tracheobronchial glands. Watkins-Pitchford (1915) aptly states that; unless at least some excess of pigmentation is found in the substance of the lung, it may be safely concluded that the individual was not the subject of pneumoconiosis in any form. The pigmented moiety of the inhaled dust is not necessarily the mischief-making factor, nor is it always increased in proportion to the amount of damage present, nor does it necessarily indicate excessive exposure to pigmented dust, for it may simply represent the usual anthracotic pigmentation common to the lungs of nearly all adults, but somewhat increased as the result of faulty elimination due to choked lymphatic exits (Watkins-Pitchford, 1915). Another distinctive feature of simple pneumoconiosis is that the tissue changes are symmetrical and uniform throughout both lungs, a feature which, theoretically at least, distinguishes the simple from the complicated pneumoconiosis.

With the proliferation of reticular cells, and ultimately the laying down of collagen in relation to the dust deposits, the lesions become definitely demonstrable to the touch, a factor of paramount importance in a legal sense, for in most countries it is only when the lesions are both visible and palpable that the presence of silicosis in a lung speci-

men becomes recognizable by law (Watkins-Pitchford, 1927). On the cut surface of such a lung the dusted foci may, therefore, stand out as palpable nodules, whereas in reality they are not nodules at all, but simply the cut ends of thickened lymphatic trunks with bloodvessels or bronchi in their centers. Watkins-Pitchford has shown (1915) that, when dissected out, these palpable lesions are really beaded strings and not discrete nodules. There has been much confusion occasioned in the minds of many investigators by failure to differentiate this simple lymphatic thickening from the more specific, discrete, so-called "silicotic nodule," to be considered presently.

The tracheobronchial lymph nodes are densely pigmented, usually jet black, a little enlarged and of rubbery consistency. Microscopically they show a heavy deposition of dust particles in the reticular cells. Fibrous nodules are not necessarily present in the nodes; the usual type of induration consists of a more or less diffuse hyperplasia of reticular cells, more marked in the medulla than in the cortical parts of the gland.

4. *The Stage of Nodulation ("Silicotic Nodule")*. In the more serious types of pneumoconiosis, notably in silicosis, there occurs a characteristic lesion of a sort quite different from the lesions described up to this point. It consists of a dense nodular growth of connective tissue formed of more or less concentric strands of collagen, sometimes forming a filigree pattern, always interlarded with narrow chinks like basketwork, always acellular in the central portions and invariably surrounded by a zone of cellular connective tissue. These nodules occur singly, in which case they are quite small, averaging about 1 mm. in diameter, but more commonly they are agminated into small composite groups of the size of a pea or occasionally somewhat larger. They are found in the parenchyma of the lung, in the subpleural tissues and in the hilus glands. Their distribution is characteristic; they always appear to arise in interstitial tissue of the lung (Mavrogordato, 1922), commonly at the entrance to the lung lobule (Simson, 1930; Irvine, Simson and Strachan, 1930), though not necessarily in relation to lymphoid tissue (Kettle, 1932). They stand discrete from bloodvessels or bronchi. Quite often composite nodules appear to replace entire lung lobules (Zenker, 1867; Watkins-Pitchford, 1914, 1915; Belt, 1929). Not infrequently, composite nodules are so thickly placed as to form a massive induration, replacing large areas of lung parenchyma. The nodules are of firm, rubbery consistency and iron-gray to black in color. The larger nodules often have a laminated appearance demonstrable to the naked eye and show thin rings, like the annual rings of a tree trunk; the intensity of the pigmentation varies from one ring to another so that it is not uncommon to find one or more rings of pale silvery color in an otherwise black nodule. In an area of conglomerate nodules these rings of lesser pigmentation lend to the specimen a peculiar naked-eye appearance which Watkins-Pitchford (1915) has designated as "fibrotic figures." On the whole, the nodular lesions are much less deeply pigmented than the perivascular and peribronchial aggregations. In distribution the nodular lesion tends to be much more irregular than the changes of the preceding phase of the reaction. It is usual to find some parts of the lung less affected (by the nodular lesion) than others; indeed, there may be only 1 or 2 nodules in a single lobe or in a whole lung (Watkins-

Pitchford, 1915). In the tracheobronchial glands the nodular lesions tend to localize in the cortex, near the capsule (Giese, 1933), in contrast to the diffuse fibrosis of the second and third phases, which has a predilection for the hilus of the gland.

The nodular lesions are of more serious consequence than the relatively innocuous lymphatic cirrhosis of simple pneumoconiosis. The economy of the lung now suffers interference. Considerable areas may be consolidated as the result of massive fibrosis, and, while this in itself is seldom sufficient to produce death, yet emphysema and embarrassment to the right side of the heart are common sequelæ and not infrequently determine a fatal issue. But what is of greater consequence, the individual is now a very poor risk, should pulmonary infection supervene.

The Nature of the "Silicotic Nodule." Concerning this nodular lesion pathologists are unanimously agreed that it is of more or less constant morphologic character and peculiarly distinctive of full-blown pneumoconiosis. But here the unanimity ceases; as to the exact etiology, pathogenesis and significance of the lesion there is great divergence of opinion. The majority of pathologists have followed in Zenker's footsteps and regarded it as a lesion produced entirely through the agency of dust. Many have taken the further step of ascribing it specifically to silica dust, and consequently it has come to be known the world over as a "silicotic nodule." A few have clung to the alternative idea which was also in Zenker's mind, that it represents an obsolete tuberculous process; others regard it as a combined effect of tuberculous infection plus excessive dust inhalation.

Were it not for the fact that pulmonary tuberculosis so often complicates pneumoconiosis, the problem of deciding the etiology of the silicotic nodule would be simplified. But the two diseases are so frequently coupled in industry that the question of the respective rôle of each has been a notoriously perplexing problem.

There is the incontrovertible fact of a high incidence of nodular pneumoconiosis in individuals whose occupations expose them to the inhalation of large quantities of silicious dust. It has been shown also that the silicotic nodule often contains appreciable numbers of silicious dust particles (Greenhow, Zenker, Watkins-Pitchford, Collis, Mavrogordato, Belt, Giese, Gardner, Klotz, *et al.*), a fact which suggests an etiologic relationship of the dust to the lesion. On the side of negative evidence in the same direction, stress has been laid on the consistent absence of histologic criteria of tuberculosis in the silicotic nodule; where there are neither giant cells nor caseation nor characteristic granulomatous reaction, most morphologists refuse to recognize the elements of tuberculous infection. Numerous attempts to demonstrate the tubercle bacillus in the silicotic nodule have failed, and in a few instances where biologic tests have been carried out, the tissues have proved negative on guinea-pig inoculation (Strachan and Simson, 1930). Furthermore, there comes from all sides the common clinical observation that many cases of nodular pneumoconiosis fail to evince the signs and symptoms of an infective process.

Numerous attempts have been made to reproduce the lesions of pneumoconiosis by the introduction of various types of dust into the tissues of experimental animals. (Ruppert, 1878; Wainright and Nichols, 1905; Beattie, 1912; Cesa-Bianchi, 1913; Mavrogordato,

1918; Gardner, 1920 *et seq.*; Gye and Purdy, 1922; Carleton, 1923; Rona, 1924; Willis, 1928; Mills, 1931; Haynes, 1931; Policard, 1931; Policard and Rollet, 1931; Kettle, 1932, 1934; Lemon and Higgins, 1932; Lemon and Feldman, 1933; Cameron and Lang, 1933; Miller and Sayers, 1934; Robson, Irwin and King, 1934.)

These experiments have proved of great value in elucidating the cytology of the dust reaction and ascertaining the relative effects of various dusts, and, while for the most part little difficulty has been experienced in reproducing the early lesions of pneumoconiosis as seen in man, *viz.*, lymphatic choking and thickening, plaque and pseudo-tubercle formation, yet the results have been singularly disappointing as regards reproduction of the well-known silicotic nodule of the human disease. Many authors have claimed experimental reproduction of "typical silicotic nodules," but careful scrutiny of their illustrations and descriptions fail to convince one that their claims are valid. Nearly all experimentalists in the field of pneumoconiosis stress the high incidence of pneumonia in dusted animals, and, from a critical evaluation of their results as a whole, it seems more than probable that the majority of fibrous lesions produced in the parenchyma of animals' lungs by experimental dusting are due in no small measure to a secondary pneumonia rather than to the dust *per se*. Thus, in the latest piece of experimental dusting to be reported (Robson, Irwin and King, 1934), the lesions claimed to be "typical, silicious, fibrotic nodules" are obviously nothing more than patches of organized pneumonia, bearing no resemblance either in morphology or distribution to the silicotic nodules of a miner's or a stonemason's lung. Strachan (1930) expresses grave doubt as to whether a true, non-infective, uncomplicated silicosis (meaning the nodular type) has yet been produced in experimental animals. The same doubt is expressed by Kettle (1934). Researchers who have injected dust suspensions intravenously or subcutaneously have produced quite definite lesions, usually ending in fibrosis, but it is not too much to say that none of these has reproduced the silicotic nodule.

The prolonged and elaborate experimental work of Gardner (1932) stands out in contrast to the rest as having attained results more comparable to the human lesions. In the lungs of some of his rabbits and guinea pigs exposed to daily dusting with particulate silica and silicates for periods up to 3 years and more, there have developed fibrous nodules quite like the fibrous knots of human pneumoconiosis, though still falling somewhat short of exact duplication. Gardner himself admits there is at least one peculiarity of his experimental nodules, namely, that they remain vascularized, which makes them differ from their human counterpart.

With this long series of experiments in the background illustrating the difficulty of reproducing the silicotic nodule, the recent successful attempt by Kettle (1934) is particularly significant. By the addition of dead tubercle bacilli to a suspension of powdered clay (aluminium silicate), the characteristic lesion was induced in guinea pigs' lungs in the relatively short period of 112 days. The illustrations accompanying Kettle's report leave no room for doubt that the silicotic nodule has at last been faithfully reproduced. The significance of Kettle's work lies, of course, in the fact that it strongly suggests the silicotic nodule to be the result of the combined effect of a dust factor plus

a tubercle factor. This bit of experimental evidence lends strong support to a view which has long been in the back of many an investigator's mind and openly expressed by not a few. Watkins-Pitchford at first (1914) took the silicotic nodule for a non-infectious lesion due solely to dust, but later (1915) he says "I now think I may have been mistaken and that these fibrotic figures, though histologically totally dissimilar to tubercles, are a pathologically unique indication of the presence of the tubercle bacillus in the silicotic lung. . . . Dr. L. G. Irvine has long held that these peculiar gray figures were due to a tuberculous infection. . . . Isolated examples of these figures are sometimes seen to be the seat of caseation, organisms have occasionally been found in them and biological tests of their contents are sometimes positive for *B. tuberculosis*." Policard (1930) says "In the immense majority of cases, if not in all, the silicotic lung is also a tuberculous lung." Irvine, Simson and Strachan (1930) make the following significant statement: "We should not think of 'simple' silicosis merely as a dust fibrosis, but as being, at least in many cases, a dust fibrosis, which from its beginning as a clinically detectable condition is linked up with an element of latent tuberculous infection." In the same article as the above quotation appear the following striking figures as to the prevalence of tuberculosis among silicotic miners in South Africa: 1923 cases were diagnosed as primary "simple" silicosis from 1917 to 1923. Of these, 543 were dead by July 31, 1929, 373 having died of tuberculosis. And Professor Loriga, of Italy (1930), adds "The infectious tubercular factor constitutes such a frequent complication as to leave the doctor almost constantly in doubt in regard to the gravity of the pneumoconiosis considered as a separate disease."

It is questionable whether those who regard or have regarded the silicotic nodule as a dust lesion (Zenker, 1867; Beck, 1895; Shattock, 1914; Watkins-Pitchford, 1914; Collis, 1915; Mavrogordato, 1922; Cummins, 1927; Gardner, 1929; Bergstrand, 1930; Böhme, 1930; Schridde, 1929; Strachan and Simson, 1930; Giese, 1931 and 1933) have justifiably ruled out tuberculosis because of the lack of giant cells, caseation and typical granulomatous reaction; for an obsolete tubercle commonly shows none of these features and surely the obsolete lesion is just as typical of tuberculous infection as the active lesion; for do not the great majority of tuberculous lesions tend to heal? Obsolete miliary tubercles of the spleen and liver are relatively common autopsy findings (Klotz, 1917) and show morphologic characters quite similar to silicotic nodules except that they contain no dust particles; but one point that the above-mentioned authors have been hard pressed to explain is the relative paucity of dust particles in the silicotic nodule. Watkins-Pitchford and Moir (1916) found by a delicate histochemical test that there was little or no foreign particulate matter in certain massive areas of nodular fibrosis in silicotic lungs and concluded that the lesions in question were, therefore, due to infection rather than to dust. As one who at first championed the silica specificity of the silicotic nodule, the reviewer (Belt, 1929) has since had cause to doubt whether certain fibroid lesions of ordinary obsolete tuberculosis could be distinguished from silicotic nodules except by reference to the occupational history of the case. This comes from a wider acquaintance with the pathology of uncomplicated tuberculosis. No

one will deny that the silicotic nodule differs from the ordinary run of healed tubercles, but the differences seem to represent only a modification of the usual process, in the direction of a more complete fibrosis, presumably caused by the presence of dust particles (Kettle, 1934).

Among others who adhere to the silica specificity of the silicotic nodule, Strachan and Simson (1930) claim to be able to trace the various steps in the development of the lesion in human cases from the simple aggregation of dust to the full-blown hyalinized knot of fibrous tissue. Their contentions are unconvincing. One palpable weakness of their presentation is that they fail to treat of the possible existence of such a thing as a healed, fibroid tuberculous lesion. The majority of lesions one sees in the pneumoconiotic lung are either of a healed character or they are obviously tuberculous (Belt, 1929), and the various stages of development of the silicotic nodule are notoriously difficult of detection unless the nodule be construed to represent the end stage of the pneumoconiotic tubercle, in which case the earlier phases of its development are often readily demonstrable.

If then, on the basis of this accumulated evidence one is prepared to admit that the silicotic nodule is really a healed tubercle modified by dust, it means that all cases of pneumoconiosis characterized by the formation in the lung parenchyma of fibrous nodules, single, conglomerate or agminated into masses (and this would take in the majority if not all clinically demonstrable cases), are complicated by tuberculous infection from the start. This is precisely the contention of Irvine (1930), Leporin (1931) and Policard (1933).

The Dangerous Dusts. Silica has long been impugned as the chief cause of industrial phthisis. The evidence against silica has been built up largely upon statistical evidence (see page 424), the reliability of which has been questioned by Landis (1919), Loriga (1930) and Kettle (1932), but accepted by most other authorities. There is also much experimental evidence to show that finely particulate, colloidal and soluble silica are capable of producing proliferative lesions in animal tissues (Gye and Purdy, Mavrogordato, Carleton, Mills, Gardner, Haynes, Kettle and Policard), but that the silicotic nodule has ever been reproduced experimentally is open to question (see page 430). In their analysis of the mineral content of silicotic lungs in South Africa, Watkins-Pitchford and Moir (1916) claim to have found 400 particles of quartz for every 1 particle of other substances. But silica is obviously not the whole story. Cummins (1931) has established the presence of silicosis among Welsh coal miners who have not been exposed to the dust of free silica, for the rock in which they work contains only silicates (Jones, 1933). Jones, who has investigated the mineral content of the lungs of some of these cases, believes the mischief is produced by sericite, a potassium-aluminium silicate, and sees grounds for regarding this substance rather than silica as the universal cause of silicosis. Haynes (1931) has shown by animal experimentation that flint, slate, aluminium hydroxid, precipitated chalk, magnesium carbonate, carborundum, wood charcoal and colloidal coal all produce proliferative lesions in guinea pigs' lungs indistinguishable from the early lesions produced by silica. Though the dust of clay (kaolin or aluminium silicate) has been pretty generally regarded as innocuous, Kettle (1934) has shown that it produces an active tissue response in guinea pigs' lungs, and by combining this

dust with dead tubercle bacilli he has succeeded in reproducing typical silicotic nodules (1934) (see page 430). Kettle (1934) also observes: "I have myself seen pleural drift, plaque formation and a moderate degree of fibrosis, that is, the accepted signs of an incipient pneumoconiosis, with such an inert substance as carbon." Asbestos is a magnesium silicate containing little or no free silica yet capable of producing serious lung lesions both in man (Cooke, 1927; Gloyne, 1930; Sparks, 1931; Ellman, 1933) and in animals (Gardner, 1931; Schuster, 1931). The first case of pneumoconiosis reported by Zenker (1867) was due to the prolonged inhalation (7 years) of powdered red oxid of iron. The anamnesis was carefully investigated and it was clear this patient had no unusual exposure to other types of dust, yet it is obvious from Zenker's illustrations that the lungs presented lesions which would now be regarded as typical silicotic nodules. except that they were red in color. Zenker regarded all types of pneumoconiosis as essentially of the same nature, save that the color of the lesions varied with the type of dust involved. Greenhow (1869) described several cases of flaxdressers' pneumoconiosis; he found the pulmonary lesions essentially the same as those of colliers', miners' and stone-masons' phthisis also examined by him, except that the flaxdressers' lungs contained less silica by chemical assay; and he concluded "The nature of the substance inhaled appears to be of secondary consequence as regards the ultimate result." Shattock (1914) says "Striking tuberculoid lesions are sometimes encountered (in the pneumoconiotic lung) and the likeness is not determined by the particular kind of material inhaled." Haythorn (1923) claims all dusts are a menace to health if inhaled to excess. Collis (1915) lays down the general principle "That dusts are more injurious as their chemical composition differs from that of the human body." If one is justified in drawing any conclusions from this diversity of data and opinion, it would be to the effect that, though silica undoubtedly constitutes a serious health hazard, its specificity as a cause of pneumoconiosis has probably been grossly overrated; that at least some of the silicates and possibly a few substances other than compounds of silicon are culpable to some degree.

The chemists have been not a little at fault in promulgating the idea of the specificity of silica in regard to pneumoconiosis. There is no satisfactory test for the presence of silica (SiO_2). By chemical assay one can only detect the presence of silicon and cannot determine in what combination the element exists, whether as a silicate, as oxid of silicon or as silicic acid; but the universal custom is to express the result of the assay as so many milligrams of "total silica" per unit of dried tissue or per unit of the ash. Many people, unfamiliar with the meaning of "total silica," have erroneously taken it to represent the amount of actual silica present in a given specimen and have, therefore, attached undue etiologic significance to silica.

The Size of the Harmful Particles. By digesting the tissue with strong acid and recovering the mineral matter, Greenhow (1865), McCrae (1913), Watkins-Pitchford and Moir (1916), Cooke (1933) and Jones (1933) have studied the morphology of foreign particles in the pneumoconiotic lung. These authors are in agreement that the majority of such particles are of the same order of size as common microorganisms. The average dimension is about 1.2μ ; particles larger than

12 μ have not been observed in the pneumoconiotic lung with the exception of asbestos particles which, quite unlike other dusts, enter the lung in the form of unusually long fibers, sometimes 100 to 200 μ in length (Gardner, 1931). Particles this large do not, however, penetrate the tissue. Recently Gardner and Cummings (1933) have shown by an ingenious experiment that particles of quartz under 3 μ are much more productive of connective tissue proliferation (liver cirrhosis) than particles of larger size.

How Do the Dusts Act? There is ample evidence to show that dangerous dusts generally stimulate reticular cells to proliferate. The mechanism of this stimulation still awaits demonstration. The old view that the hardness and sharpness of the particles had something to do with provoking the reaction has long since been discarded. From the work of Haynes, Mavrogordato and Gardner, considerable importance attaches to the reaction which the various dusts call out on the part of the phagocytes. Dusts which are more actively phagocyted are, in general, more readily eliminated from the lung, either by expectoration or by passage through the lymphatic exits to the hilus. Dusts which provoke only a sluggish reaction on the part of the phagocytes, notably stone dust (Lauche, 1930), tend to congest the lymphatic channels and to remain more or less permanently incarcerated in them. Mavrogordato states: "Dusts that make mischief are dusts that accumulate. Dusts that are eliminated are dusts that produce a marked initial reaction." And Haynes concludes, "The intensity of the initial reaction to a dust is in inverse ratio to the degree of eventual damage caused by the dust." Gardner believes that intimate contact between silicious dust and connective tissues eventually leads to proliferation of the latter. Against this contention we have the well-known fact stressed by numerous authors that large amounts of particulate silica may apparently remain for years in the human lung without provoking any appreciable reaction.

Of recent years many investigators have swung to the view that silica undergoes a slow dissolution in the tissues, thereby liberating a toxic substance which by its injurious effect upon reticular cells stimulates them into excessive, reparative proliferation. The work of Gye and Kettle has perhaps done most to promote this view; they first demonstrated the toxicity of soluble silica, then observed that powdered quartz produced the same effect but required a longer time; they presumed that in the interval part of the quartz had gone into solution. The reviewer (Belt, 1929) thought to have adduced evidence of the slow solution of silicious particles in the human lung, but has since come to question the validity of his earlier deductions. Working on the hypothesis that silica is soluble in the tissues, Heffernan has elaborated physicochemical theories to explain the injurious effect. But it may safely be said that the solubility of silica in the tissues has not yet been satisfactorily demonstrated (Gardner, 1932).

Perhaps the most deleterious *modus operandi* of dust is its action as a carrier or vehicle for pathogenic organisms, facilitating their entrance into the lungs (Landis, 1919), for the rôle of secondary infection is coming to be regarded as of greater importance than the rôle of dust *per se* in the production of pneumoconiosis (Irvine *et al.*, 1930; Kettle, 1934). Mavrogordato (1926) makes the significant statement that the dust concentration may be an adequate measure of risk of pneumoconiosis

when dust concentration is high, but it is not so adequate when dust concentration is low, as it is nowadays in most industries, for the factor of tuberculosis may be dominating the situation.

Haldane (1913), Mavrogordato (1922), Carleton (1923) and Haynes (1931) have assembled evidence that certain relatively innocuous dusts may forestall the evil effects of more harmful dusts if inhaled at the same time. For a discussion of this moot question the reader is referred to Kettle (*Brit. Med. J.*, 1932).

Factors Contributing to the Development of Pneumoconiosis. The integrity of the upper air passages and the efficiency with which inhaled dust is filtered out before reaching the lungs is of great importance. Mouth breathers tend to develop pneumoconiosis more rapidly than those who breathe through their noses (Watt *et al.*, 1916). Since pneumoconiosis is primarily a disease of the pulmonary lymphatic apparatus, it follows that any preëxisting disorder of this apparatus predisposes to a more rapid development of the condition, given adequate exposure to dust. Gardner (1924) states that a subject whose pulmonary drainage is already impaired by chronic or healed tuberculosis of the tracheobronchial glands should develop silicosis more rapidly than one whose nodes are normal. Lanza (1933), while refusing to believe that individual susceptibility plays any appreciable part in the etiology of silicosis in otherwise normal individuals, stresses the importance of preëxisting lung disease, especially tuberculosis and incipient pneumoconiosis other than silicosis, as the factor which tends to hasten and aggravate silicosis. Age is also a factor; according to the Picher studies (quoted by Lanza, 1933), those who started mining after 40 years of age had an average of only 7.83 years of employment. Lanza also states that Wassermann-positive individuals develop silicosis more rapidly than the Wassermann-negative group and their disease runs a more rapid course.

Duration and Progress of the Severe Pneumoconioses. Pneumoconiosis is generally regarded as a disease characterized by extreme chronicity. Most authors are agreed that it takes from 4 to 20 years' exposure to relatively heavy concentrations of dust; and that even longer exposure may fail to produce the disease. South African experience shows that, in the case of those affected, the mean duration of exposure before the disease is detected is about 12 years (Mavrogordato, 1930); that the average expectancy of life of a case of silicosis when first detected is 13.66 years; and that the average duration of the second stage is 7 years (Irvine, Strachan and Simson, 1930). There is great variation in progress from case to case, but in the majority the disease tends sooner or later to advance and continue to do so even after the victim ceases his dusty occupation.

A few examples have occurred of a rapidly progressive pneumoconiosis which have been regarded and recorded as cases of acute silicosis (MacDonald, Piggot and Gilder, 1930; Chapman, 1932; Kilgore, 1932); but cases of this kind which have come to autopsy have proved to be instances of acute tuberculosis enhanced no doubt by the silica present (Kettle, 1932; Gardner, 1933). Gardner (1933) made a pathologic examination of 15 such cases and concluded: "Although there is histological evidence of silicosis, atypical in character, it seems doubtful whether there is justification for describing the process as acute."

It will be remembered that the majority of cases are considered to be infective from the beginning (see page 431), and Strachan and Simson (1930) express a generally accepted dictum when they say "All silicotics, if they live long enough, die of tuberculosis."

Pneumonoconiotic Tuberculosis. The combination of pneumonoconiosis and tuberculosis does not necessarily imply an acute and dramatic pulmonary tuberculosis (Kettle, 1934). The "infective" silicosis of South Africa is a slowly progressive lesion in which necrosis and fibrosis proceed hand in hand with a preponderance of the latter (Irving *et al.*, 1930). Landis (1919) says that tuberculosis commonly runs a latent and more prolonged course in silicotics than in ordinary hospital patients, and Collis in his comprehensive review (1915) mentions that some authorities claim tuberculosis, when implanted on silicosis, progresses more slowly than ordinary tuberculosis, though he himself was of the opposite opinion. Gardner (1924) found that the course of a primary inhalation infection with virulent tubercle bacilli (in guinea pigs) becomes more chronic as a result of subsequent inhalation of granite and carborundum dust; the death of the animal is postponed and the pulmonary lesions are characterized by fibrosis. There can be no doubt, however, that when the silicotic becomes an overt, clinical case of tuberculosis it means that the infection has gained the upper hand, and the expectancy of life is then quite short.

All authorities agree that tuberculosis as a complication of pneumonoconiosis runs an atypical course and is much more difficult of clinical detection than ordinary, non-occupational tuberculosis. Thus, the pneumonoconiotic modification of the disease commonly occurs at a later age period than is usual, that is, in middle or advanced life, and in persons who generally have no constitutional or hereditary predisposition; the sputum is not so copious nor as likely to contain tubercle bacilli; hemoptysis is rare; fever and nightsweats are usually absent; emaciation is little in evidence and the localization of pulmonary lesions is seldom apical (Collis, 1915).

Similarly, the pathologic picture differs materially from that of uncomplicated tuberculosis. The conio-phthisic lung is typically dry, dusty and fibrotic, often with little or no evidence of caseation or the usual cellular reactions of tuberculosis. It is a pathologic process which runs to an unusual degree of fibroid healing and at the same time to an unusually wide dissemination. While this is the classical picture, it must be remembered that pneumonoconiotic tuberculosis, like ordinary pulmonary tuberculosis, is a protean disease capable of wide variations in its anatomic manifestations.

Pneumonia as a Complication of Pneumonoconiosis. Acute respiratory infection is a common sequel to dust inhalation. Collis (1915) points out "the excessive mortality from pneumonia occurs at those earlier age periods which represent initial exposure." If and when infection of the pneumonoconiotic lung takes place, the individual is at a distinct disadvantage, for the blocked lymphatics prejudice the lung's ability to deal with infection (Mavrogordato, 1922). Strachan (1930) states that in cases with prolonged exposure to mine dust, though the specific lesions of silicosis may not yet have developed, an acute pulmonary infection, such as lobar pneumonia, is often followed by non-resolution, organization and fibrosis. Haythorn (1918) has shown that a simple pneumonoconiosis of anthracotic type has a very unfavor-

able influence on the course of an attack of pneumonia, impeding resolution and leading to serious complications.

Factors Relating to the Tuberculous Affinity of the Dusty Lung.

An excessive incidence of tuberculosis in relation to pneumoconiosis might be expected on the following grounds: They are both inhalation diseases; they have a common portal of entry and a common predilection to localize and spread in the pulmonary lymphatic apparatus (Shattock, 1914); both are dealt with by the same protective mechanism, namely, the dust phagocyte (Gardner, 1924). Dust particles act as carriers, facilitating the entrance of the ubiquitous tubercle bacillus into the lung (Landis, 1919). People exposed to dust hazards frequently work under wet conditions which favor the survival and transference of infective organisms (Mavrogordato, 1926; Beattie, 1912). People exposed to dust hazards are also frequently exposed to a greater risk of infection because of open cases of tuberculosis among their fellow workmen (Mavrogordato, 1926). A large proportion of persons exposed to dust hazards work underground where the survival and dissemination of pathogenic organisms is facilitated because of moisture and warmth and the absence of sunlight (Landis, 1919). Cesa-Bianchi (1913) caused guinea pigs to inhale various factory dusts, including talc, coal dust, cement and sand, then infected the animals with a strain of tubercle bacilli of low virulence; all his dusted animals, regardless of the type of dust used, died of pulmonary tuberculosis, while the controls were unaffected.

Gye and Kettle (1922) demonstrated that silica-soaked necrotic tissue was a medium favorable to the growth of tubercle bacilli *in vivo*. Kettle (1932) produced subcutaneous lesions with silica, shale, clay and asbestos dusts, then showed that tubercle bacilli injected intravenously localized and multiplied inordinately in these lesions while the presence in the tissues of carborundum, wellingtonite, iron oxid, carbon, coal, marble, silica-free mine dust and iron-coated silica was apparently a matter of indifference to the organisms. Price (1931) found sodium silicate definitely accelerated the growth of tubercle bacilli *in vitro*.

Gardner (1924) found that a previous exposure of animals to more or less prolonged inhalation of granite, carborundum and marble dusts rendered the lungs more susceptible to subsequent infection with the tubercle bacillus. He regarded this effect as due to obstruction of the pulmonary lymphatics. Of even greater significance as regards its application to the problem of human coniotuberculosis was Gardner's later work (1929), in which he tested the effects of various dusts on partially healed tuberculous lesions in guinea pigs' and rabbits' lungs; these experiments demonstrated that 73.6% of quartz-dusted, 31.8% of carborundum-dusted and 26.3% of granite-dusted animals showed marked reactivation of their tuberculous lesions, while most of the control animals and those dusted with marble and soft coal went on to complete healing. On the basis of these results Gardner thinks it likely that in the majority of cases coniotuberculosis represents an endogenous reinfection resulting from the reactivation (by silicious dust) of old, quiescent lesions so commonly present in the average, white, adult individual.

Willis (1922) found that experimental tuberculosis developed somewhat more extensively in the lungs of animals previously exposed to coal dust than in those of normal animals.

Mavrogordato (1926) showed that guinea pigs and rats which had inhaled mine dust were prone to develop pulmonary tuberculosis following intraperitoneal inoculation with tubercle bacilli, whereas control animals were not similarly affected by such an inoculation. Coal dust inhalations did not protect guinea pigs from developing pulmonary tuberculosis after intraperitoneal inoculation of tubercle bacilli. As regards coal dust, the results of Cesa-Bianchi, Willis and Mavrogordato are at variance with those of Wainright and Nichols (1905), in whose hands this type of dust protected rabbits' lungs from the ravages of tuberculosis.

There is more or less general agreement that coalminers suffer less from tuberculosis than the average of occupied males. The experimental work of Cummins and Weatherall (1931) would provide some explanation of this finding in that they were able to show that anthracite coal dust has the power of adsorbing the active principle of tuberculin.

The Diagnosis of Pneumoconiosis. It is perhaps illustrative of the difficulty often encountered in establishing the presence of pneumoconiosis that practically all who have to do with the diagnosis of the condition emphasize the importance of taking into account all available information concerning a case before an opinion is expressed. In many instances an accurate diagnosis may be arrived at during life from a consideration of the occupational history, the physical and roentgenologic findings. And after death a naked-eye examination of the lungs will often suffice to establish the case. Pathologists in the South African mining fields contend that in cases which come to autopsy it is possible to give a definite opinion regarding the degree of silicosis present from the appearances found in the macroscopic specimen alone; in fact, it is only rarely that resort is had to microscopic analysis (Strachan and Simson, 1930). But in Europe and America such confirmatory evidence as may be obtainable from laboratory investigations is often required for compensation purposes.

One swallow does not make a summer, no more than one nodule will make a case of silicosis. There must be visible and palpable fibrosis, and the lesions must be present in such numbers that, on the average, at least one will appear in each 5 cm. squared of the divided lung substance (Watkins-Pitchford, 1927).

The greatest difficulty encountered by the pathologist is to assess the rôle of dust in complicated cases, especially those in which there is much fibrosis, part or all of which may be due to causes other than dust. The changes characteristic of the early phases of pneumoconiosis should not be overlooked in arriving at a diagnosis. Choking and thickening of the pulmonary lymphatics by dust particles is a necessary preliminary to the more advanced lesions (Mavrogordato, 1922) and provides an easily recognizable criterion of the presence of pneumoconiosis, yet sometimes it seems to be overlooked in the pathologic analysis of certain complicated cases, and often enough more importance is attached to the chemical assay of the tissue than to the condition of the lymphatics. It is hardly to be expected that dust could be accountable for extensive changes in the parenchyma of the lung if it has not yet produced the lymphatic choking which is recognized to be its initial effect. There is perhaps too great a tendency to regard lung fibrosis by and large as a specific effect of dust. Fibrosis is essentially a non-specific change and may be called forth in the lung by any number of different agencies, but especially by organizing

pneumonia, chronic interstitial pneumonia (Lauche, 1928) and tuberculosis. Gardner (1932) believes chronic pneumonias to be quite common in man as well as animals, and Mavrogordato (1926) and Strachan and Simson (1930) have stressed the frequency with which this condition complicates pneumoconiosis. Kettle (1934) has shown very convincingly how closely the lesions of pneumoconiosis may be simulated by non-occupational fibroid phthisis.

Thus, when ordinary histologic methods of analysis fail to make the necessary distinctions, recourse is had to methods of demonstrating the amount and character of foreign particulate matter present in the lesions in question.

The polarizing microscope is a useful adjunct for demonstrating birefringent mineral particles in histologic preparations. It is frequently possible to gain a rough idea of the amount and distribution of silicious particles, and thereby to establish the presence of a dust factor by this means alone. The advantages and limitations of the instrument are set out by Watkins-Pitchford and Moir (1916) and Belt (1929).

More accurate estimations of the dust content of the lung tissue may be obtained by chemical assay of the "total silica" present. As has been pointed out elsewhere, "total silica" is simply an expression of the amount of the element silicon and gives no indication as to what form of silicon compound or compounds were present. But since most of the harmful dusts are either oxids of silicon or silicates, the "total silica" is a serviceable index of the dust factor in a given specimen of diseased tissue. The "total silica" content of normal lung varies from 0 up to 0.2% of the dry weight (King, 1928). Figures in excess of the normal range may, therefore, be taken to indicate dust disease (Sladden, 1933; McNally, 1933; Kettle and Archer, 1934), but will not aid in distinguishing between silicosis and silicatosiis.

There is one possible fallacy worthy of mention in the interpretation of "total silica" assays. Woskressensky (1898) demonstrated that the "total silica" content of normal tracheobronchial glands increases with age, from *nil* in the newborn to the surprisingly high proportion of 34 to 55% of the ash in elderly individuals. This is simply the result of life-long inhalation of ordinary house and street dusts, which are partly constituted by clay and sand particles. Confirmation of Woskressensky's early observations will shortly be published by Belt and King. Thus all ordinary adults have a silicosis or a silicatosiis as well as an anthracosis of the tracheobronchial lymph glands and to some extent of the pleura as well. In the ordinary course of events, these "normal" dust deposits are confined to lymph glands and pleura and do not locate in the substance of the lungs. If, however, there are scars in the lung parenchyma, as from a childhood tuberculous infection, the "normal" dusts will collect around such a scar, as witness of which it is observed that old tuberculous lesions are invariably surrounded by a zone of anthracotic pigmentation. Therefore, if peribronchial glands or disproportionately large areas of pleura or localized childhood scars be included, as might easily happen, in the block of suspected lung submitted for chemical assay, the resulting "total silica" estimation will likely include considerable quantities of "normal" silicious dust, and a high percentage of "total silica" in the ash may, therefore, be misinterpreted as indicating silicosis or silicatosiis. For this reason it is necessary, if reliance is to be placed on chemical assay

as an aid in diagnosis, to submit several blocks of the suspected lung, and to know from what part of the lung each block was taken.

A third laboratory method of investigating the mineral content of tissues is microincineration, described by Policard (1929), Schultz-Brauns (1929), Scheid (1932) and others; it is a modification of the early technique of Greenhow (1865), and has the advantage of enabling a microscopic study of the physical relationship of dust deposits to the tissue changes. It is possible by this means to determine the dust content of individual lesions more accurately than by the use of the polariscope on ordinary histologic preparations. From an ordinary paraffin block of tissue, serial sections 5 or 6 μ thick are cut in groups of 3; of each group, 1 is stained with hematoxylin and eosin in the usual way, while the other 2 are mounted unstained on glass slides and heated for an hour to 500° C. in a specially constructed oven. The heating drives off all the organic constituents of the tissue section, leaving the inorganic and mineral residue lying *in situ*. One of the ashed sections is then treated with concentrated hydrochloric acid, which removes calcium, iron and phosphorus compounds, leaving silica and silicates as well as a few other substances which occur only in traces. Then by comparing this slide with the stained section the deposits of residue are readily related to the histologic detail. This procedure will demonstrate prettily the amount of silicious material in a given lesion; it does not, however, always serve to distinguish infective from non-infective dust lesions (*contra* Irwin, 1934) for tuberculous lesions in the coniotic lung, for example, are often heavily strewn with silicious particles (Gardner, 1920; Belt, 1929). By microincineration it is possible to exclude silicious dust as the cause of certain lesions, for if there is any silicious material present in a lesion, microincineration is sure to demonstrate it, and in the absence of any such material the lesion must obviously owe its existence to some other agency. Microincineration is also of assistance in judging whether infective lesions are antecedent to or coincidental with dust exposure. If, in a conio-phthisic lung, it can be shown that foreign particulate matter is scattered through tuberculous lesions, then the case may be regarded as one of coniotuberculosis; but if, on the other hand, tuberculous lesions or fibroid lesions without evidence of active tuberculosis are shown to contain no foreign particulate matter, then such lesions are to be regarded as belonging to a process which antedated the dust exposure; for it has been established that any infective lesion of the lung, tuberculous or otherwise, which develops during the course of or following dust exposure will contain appreciable quantities of the dust, because dust-laden phagocytes take an active part in any superimposed inflammatory reaction (Gardner, 1920).

Summary and Conclusions. From a review of the present knowledge of pneumoconiosis it may be concluded:

1. There is no conclusive evidence to show that silica has a specific action on the tissues.

2. Certain of the silicates and perhaps other substances may produce similar if not identical effects.

3. Infection, and especially tuberculous infection, is a more serious factor in the development of the disabling pneumoconioses than dust *per se*.

4. Dust modifies pulmonary tuberculosis in a twofold manner; it

increases the fibrous response, thus promoting chronicity, and at the same time it increases the tendency of the infection to spread.

5. The so-called "silicotic nodule" has probably never been reproduced experimentally except by the synchronous inoculation of tubercle bacilli with dust.

6. The "silicotic nodule" is probably always a tuberculous lesion, modified by dust.

7. Chemical assay of suspected tissues is open to the criticism that it does not reveal the proportion of silica to silicates.

8. There is probably no such thing as acute silicosis.

9. Evidence regarding the action of coal dust on the tissues and its influence on tuberculous infection is conflicting.

T. H. B.

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HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
 BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF NATIONAL INSTITUTE OF HEALTH, UNITED STATES PUBLIC HEALTH SERVICE,
 WASHINGTON, D. C.

NEWER ASPECTS OF TYPHUS FEVER.

TYPHUS and typhus-like diseases have in recent years attracted considerable attention in various parts of the world, and out of the

studies that have been prosecuted there has developed a new orientation on the subject, largely as a result of the work of American observers. The study of the infection in the United States has been of particular interest. The evidence indicates that typhus is quite prevalent in some of the states bordering the Gulf of Mexico and in those of the South Atlantic group—in other words, from Texas to Maryland, with scattered cases along the remainder of the Atlantic Seaboard. For many years the knowledge of the transmission of typhus—based on observations made in the Old World—had been regarded as quite satisfactory. It was regarded as an infection of man, always derived from man through the body louse, the louse having fed on and having been infected from another case of the disease. Some 10 years ago, to be sure, Maxcy cast some doubt on the views of transmission then held by pointing out differences in epidemiology between typhus as known in Europe and typhus as it occurs in the southern United States. Briefly, he showed that typhus in the United States was a summer and fall disease as against its prevalence in winter and spring in Europe, that it apparently never spread from person to person, that it was not particularly prevalent in institutions—indeed, that institutions had a noteworthy immunity—and, finally, that the victims rarely, or never, presented evidence of infestation with body lice. Within the past 3 years, Dyer and his associates, of the United States Public Health Service, and Mooser and his associates, in Mexico, have studied the subject intensively from the point of view of transmission and present an explanation of the facts observed by Maxcy and others that involves an entirely new conception of the mode of transmission. In these studies, suspicion was attracted first to rat fleas and to the rat, since it had been observed that in endemic foci of the disease rat-infested premises often were associated with the development of typhus infection. Laboratory examination of rats and rat fleas taken from such premises actually showed the presence of the typhus virus. The connecting link between the typhus-infected rat and man is apparently the flea (*Xenopsylla cheopis*), which it so happens is also the carrier of the bubonic type of plague.

Flea transmission was proven by the rat-to-rat transfer of infection by means of the flea. Not only do these studies offer an explanation of the observed facts in relation to typhus as it occurs *endemically* in the United States and in other parts of the world, but they justify an entirely new hypothesis to account for the prevalence of *epidemic* typhus. Briefly, this view is that in many communities typhus lies relatively dormant as an infection among rodents, propagated among them by fleas, and is communicated occasionally to man through the same parasite. If this transfer of the infection to man should occur in a louse-infested population, and other conditions are favorable, the disease then may spread among the human population as a louse-borne infection. This explanation seems to meet the facts with respect to epidemic typhus.

It is obvious that if the views referred to above are sound (and there are many reasons for believing that they are) our efforts to combat typhus—hitherto directed entirely against human body lice—must take account of the rat and his parasites.

Rickettsiæ, constantly associated with the disease in animals and in

lice, are also present in typhus-infected fleas. These bodies, or bodies indistinguishable from them, have been propagated in tissue cultures, although they have resisted efforts at cultivation in artificial media. The recent immunologic studies of Zinsser have furnished additional evidence of their etiologic significance.

The clinical aspects of typhus as it occurs in the United States are of special interest, since cases are often overlooked. The onset is usually sudden, with chill and fever, aching pains and often with pronounced, persistent headache. The fever lasts about 14 days, deferescence usually taking place by rapid lysis. On about the fifth day a rash appears which may be scanty or abundant and which usually develops first over the lower ribs or upper abdomen. It consists of small discrete red macules, not shotted and not itching. In severe cases it may spread to practically the whole of the cutaneous surface, but usually spares the hands and feet. The face and neck are seldom involved. The rash usually begins to fade 4 or 5 days after its appearance.

An important aid in diagnosis is derived from serologic investigation, since the blood serum in this disease almost invariably shows a positive reaction with the well-known strain of *B. proteus* in general use for the diagnosis of members of the typhus group of infections. This serologic test, of great value though it is, does not serve to differentiate the condition from spotted fever of the Rocky Mountain type, and possibly other closely associated diseases of the same type.

The prognosis of typhus as it occurs in the United States is, in general, very good. The death rate certainly is not more than 1 or 2%.

Treatment appears to be symptomatic, with special emphasis laid on the giving of adequate amounts of fluid and the maintenance of general nutrition. Convalescence usually is fairly prompt.

G. W. McC.

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ORIGINAL ARTICLES.

THE MECHANISM OF THE INCREASED FRAGILITY OF THE
ERYTHROCYTES IN CONGENITAL HEMOLYTIC JAUNDICE.

BY RUSSELL L. HADEN, M.D.,
CHIEF OF THE MEDICAL DIVISION, CLEVELAND CLINIC,
CLEVELAND, OHIO.

CONGENITAL hemolytic icterus is characterized clinically by anemia, non-obstructive jaundice and enlargement of the spleen. The erythrocytes show constant microcytosis (small diameter), an increase in reticulocytes and a decreased resistance to hypotonic salt solutions. The anemia is caused by the increased blood destruction resulting from the abnormal fragility of the red cells, the jaundice is due to the rapid formation of bile pigments from the released hemoglobin beyond the excretory capacity of the liver; the spleen is enlarged because of the great increase in its phagocytic activity; the reticulocytosis is an expression of the overstimulation of the bone marrow in attempting to compensate for the rapid destruction of erythrocytes. The anemia, the jaundice, the splenomegaly and the reticulocytosis are thus all secondary to the increased blood destruction.

The two characteristic changes in the erythrocyte, microcytosis and increased fragility, have been noted by all careful students of the disease, although there is no unanimity of opinion concerning the cause and the interrelation of these two findings. The observation of microcytosis has usually been based on finding a decrease in the mean cell diameter on measurement or the obvious smallness of the cells on examination of a stained blood film. Little attention has been given to the actual volume of the cell, since very few measurements of the mean corpuscular volume and thickness have been made.

Naegeli¹ found in 11 patients a mean corpuscular volume of 100 cubic microns (his normal, 88 cubic microns), von Boros,² a mean of 85 in 8 cases (his normal, 91), and Gänsslen,³ a volume of 92, 95 and 111 cubic microns in 3 cases. The diameter of the mean cell is decreased out of proportion to the change in volume, so it is apparent that the thickness of the cell must be increased, and the cell must tend to a spherical instead of biconcave shape. Naegeli¹ thinks that the presence of erythrocytes of decreased diameter and increased thickness is a constant and fundamental variation from normal in patients with congenital hemolytic icterus, representing the inherited feature of the disease and indicating a distinct type of human species. Such cells he designates spherocytes to denote their characteristic globular form and as synonyms for congenital hemolytic anemia he uses the terms, "spherocyte anemia" and "globe-cell anemia."

Other observers have said little about the increased thickness of the erythrocyte and offer varying explanations for the microcytosis. Chauffard,⁴ who first noted this type of cell, regarded the small size as well as the increased fragility as an expression of the lessened vitality of the cells. Meulengracht⁵ is inclined to the view that the microcytosis and increased fragility are regeneration phenomena secondary to the increased bone-marrow activity. Von Boros² finds thick microcytes in conditions other than congenital hemolytic jaundice, and hence does not regard them as characteristic of the disease. Gänsslen³ considers the primary defect in the marrow, making it incapable of supplying cells of normal size and resistance.

While microcytosis is almost an invariable finding, only Naegeli and von Boros have considered the frequency and degree of spherocytosis. Naegeli records no measurements of cell thickness in his cases, although he recognized this as increased. Von Boros⁶ gives a line chart for calculating cell thickness from the measured diameter and corpuscular volume and also evolves a formula for calculating the volume of the mean cell from the measured mean diameter when changes in the diameter and thickness are proportional and parallel. To indicate the degree of change in thickness he suggests a "thickness index" which is calculated by dividing the mean corpuscular volume (as determined directly from the red cell count and the hematocrit reading) by the mean corpuscular volume (as calculated by his formula from the measured mean diameter) when the decrease in thickness is proportional to the decrease in diameter. Since this index records not only the thickness relative to normal but considers the volume as well, it is best called the "volume-thickness index." The rather laborious calculation of this index by the method of von Boros may be simplified by using a nomogram⁷ in which the volume index (volume of the mean cell relative to normal) corresponding to any mean cell diameter is indicated. Thus, from the nomogram the volume index corresponding to a mean

cell diameter of 6.41 microns is 0.581 if the thickness is decreased in the same proportion as the diameter. This figure multiplied by 90, the normal mean corpuscular volume in my series, gives a calculated mean corpuscular volume of 52 cubic microns for a mean cell diameter of 6.41 microns. The measured mean corpuscular volume in this instance was 78 cubic microns. The volume-thickness index (V.-T. I.) is then $78/52 = 1.50$. Von Boros calculated this index in 8 patients with congenital hemolytic icterus and found it increased in 4 and within normal limits in 4.

To determine the frequency and degree of spherocytosis in my series of cases of congenital hemolytic jaundice, I have measured the mean corpuscular volume, the mean cell diameter and calculated the volume-thickness index in 10 patients with an active form of the disease and in 2 patients after splenectomy (Table 1).

TABLE 1.—SIZE AND SHAPE OF ERYTHROCYTES IN CONGENITAL HEMOLYTIC JAUNDICE.

Patient.	Diagnosis.	Measured mean erythrocyte volume (A), cubic microns.	Measured diameter, microns.	Calculated thickness, microns.	Calculated mean erythrocyte volume from measured diameter (C), cubic microns	Volume-thickness index, A/C.
1	Normal	90	7.70	1.95	90	1.00
2	Congenital hemolytic jaundice	160	6.41	4.75	52	3.10
3	Congenital hemolytic jaundice	77	6.40	2.40	52	1.50
*		78	6.67	2.25	59	1.32
4	Congenital hemolytic jaundice	90	6.18	3.00	47	1.92
5†	Congenital hemolytic jaundice	87	6.55	2.60	55	1.60
6	Congenital hemolytic jaundice	110	6.50	3.30	54	2.00
7	Congenital hemolytic jaundice	87	6.94	2.30	66	1.35
8	Congenital hemolytic jaundice	90	7.05	2.30	68	1.32
9	Congenital hemolytic jaundice	86	7.18	2.18	70	1.23
10	Congenital hemolytic jaundice	108	7.41	2.50	79	1.36
11	Congenital hemolytic jaundice	102	7.18	2.52	70	1.45
12	Congenital hemolytic jaundice	72	6.10	2.75	45	1.60
13	Obstructive jaundice	93	8.17	1.80	105	0.89
14	Obstructive jaundice	91	8.57	1.60	126	0.73
15	Pernicious anemia	130	8.84	2.10	140	0.93
16	Pernicious anemia	135	8.89	2.20	141	0.96
17	Idiopathic microcytic anemia	63	7.07	1.60	70	0.90
18	Idiopathic microcytic anemia	59	6.68	1.70	59	1.00

* Same patient 3 months after splenectomy.

† Six years after splenectomy.

In every instance the mean cell diameter is decreased and the volume-thickness index is increased, although the mean corpuscular volume is variable. In simple microcytic anemia and pernicious anemia the index is normal; in obstructive jaundice it is decreased, since the mean diameter is usually increased without a correspond-

ing increase in mean corpuscular volume. The characteristic findings are best illustrated by a diagram showing a cross-section view of the mean cell in these different clinical conditions (Fig. 1). In 2 patients studied after splenectomy the microcytosis and increased volume-thickness index have persisted, although the jaundice and anemia have disappeared.

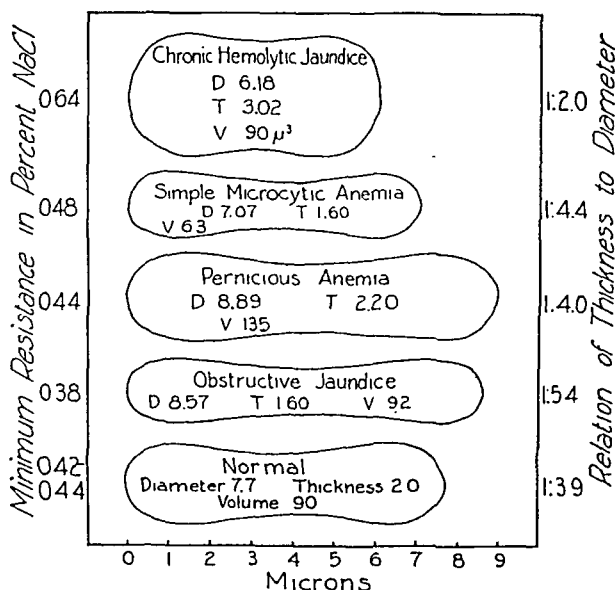


FIG. 1.—Cross-section and measurements of mean erythrocyte in different clinical conditions.

It seems apparent from my results that Naegeli's conception of microspherocytosis as the fundamental and probably constant in-born error in this disease seems the correct one. This abnormal shape of the red cell evidently represents an anatomic variation from normal, just as do the tower skull and other physical abnormalities frequently observed in congenital hemolytic jaundice. It is also apparent that the determination of the volume-thickness index is a most valuable procedure in the diagnostic study of doubtful cases of congenital hemolytic jaundice, since the index is constantly increased here and rarely, if ever, in other confusing clinical conditions. The persistence of microspherocytosis after splenectomy is of importance also in evaluating this variation from normal in the shape of the cell as the primary feature of the disease.

Although the microspherocytosis and the increased fragility are constant and the only fundamental features in the disease, no one has proved a direct relationship between these two phenomena. Naegeli¹ regards both as constitutional and caused by the fundamentally different cell structure; Gänsslen⁸ thinks both are evidence of a primary defect in the bone marrow, and suggests that

the microspherocytes by reason of their increased thickness absorb water more readily from a hypotonic solution. Von Boros points out, however, that the capacity for absorption is less, instead of more, since such cells have a small surface in relation to volume. Meulengracht⁵ has discussed the parallelism of the two findings, but concludes there is no relation between them. I have made some experiments which indicate that the increased fragility is dependent on the spherocytosis or altered shape of the cells which affords a possible explanation for the increased hemolysis characteristic of the disease.

In the lower animals the volume and diameter of the erythrocytes varies greatly, while the thickness is much the same. Emmons⁹ measurements of all dimensions of the red cell in the dog, rabbit, cat and goat, and Vallery-Radot's¹⁰ determination of the resistance of the red cells to hypotonic salt solutions for the same group of animals, are summarized in Table 2 and shown graphically in cross-section in Fig. 2. As the cell changes toward a globular shape in different species, the resistance of the cells to hypotonic saline solution decreases in almost direct proportion, so there seems a definite relation between the tendency to spherocytosis and increased fragility in lower animals.

TABLE 2.—RELATION OF SIZE AND SHAPE OF ERYTHROCYTES TO RESISTANCE TO HYPOTONIC SOLUTIONS.*

	Diameter.	Thickness.	Volume.	Relation of thickness to diameter.	Resistance, % NaCl.
Man	7.8	1.84	88	1 : 4.2	0.42-0.48
Dog	7.2	1.70	69	1 : 4.2	0.50-0.54
Rabbit	6.6	1.84	63	1 : 3.6	0.52-0.54
Cat	5.6	1.75	43	1 : 3.2	0.60-0.66
Goat	4.0	1.95	25	1 : 2.1	0.72-0.74

* Measurements from W. F. Emmons;⁹ fragility tests from Vallery-Radot.¹⁰

To obtain further information on this point I have determined the shape of the red cell of man when placed in hypotonic salt solutions. Heparinized blood was pipetted in aliquot amounts into a series of graduated centrifuge tubes, quickly centrifugalized and distilled water in varying amounts was added to the supernatant plasma. After thorough mixing, the cells were again suspended in the diluted plasma, the tubes allowed to stand for 1 hour, films made on cover glasses from the diluted blood and tubes again were centrifugalized to determine the changes in volume of the cells. A red cell count was done and the mean corpuscular volume for each dilution was calculated. The tube in which hemolysis began was noted. The mean cell diameter in each tube was determined by measuring 200 cells on the stained film and the thickness cal-

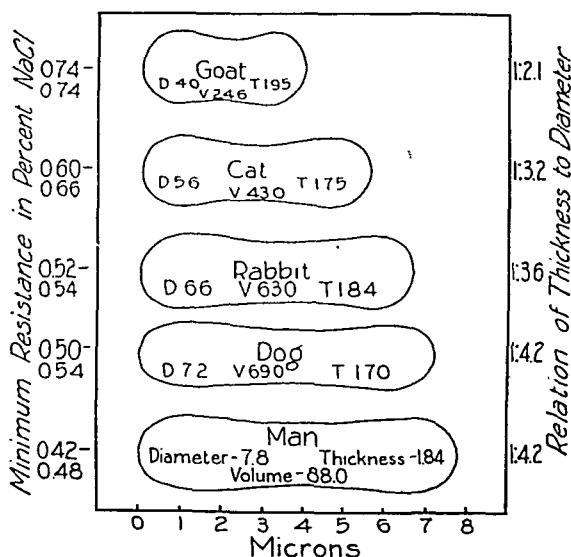


FIG. 2.—Cross-sections and measurements of the mean in different animals in relation to fragility.

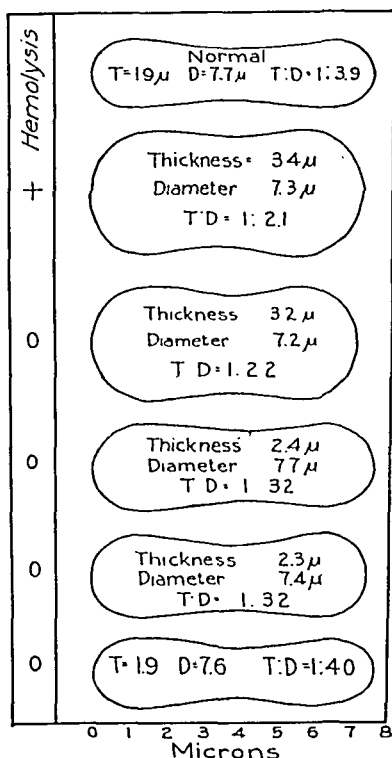


FIG. 3.—Changes in the shape and measurements of the mean erythrocyte of normal blood on the addition of varying amounts (Table 3) of distilled water to the plasma.

culated from von Boros' chart. The progressive change in shape in the cells of normal blood so treated is shown in Fig. 3. The changes in diameter are slight, while the variation in volume is slight, so the cells become thicker and globular. At a certain point hemolysis begins. Hamburger¹¹ found long ago that the erythrocytes of the horse and dog decrease in diameter as the plasma is diluted with distilled water, and pointed out that the cells so treated become globular. Ponder¹² found a similar decrease in the diameter of the cells of man in hypotonic salt solution. Pijper,¹³ on the contrary, reports an increased diameter in hypotonic solutions. I can find on record no measurement of the volume and thickness of the erythrocytes of man in relation to diameter when placed in hypotonic salt solutions.

Since the characteristic variation of the erythrocyte from normal in congenital hemolytic jaundice is a decreased diameter with increased thickness, it is apparent that much less dilution of the plasma in which such cells are suspended should be necessary to bring them to the shape at which hemolysis takes place. For, at the beginning, the shape of the cells already corresponds to one of the stages through which a normal blood must pass when placed in successive dilutions of plasma. The experiment made with normal blood was repeated with blood from a mild and from a severe case of congenital hemolytic jaundice (Table 3 and Fig. 4).

TABLE 3.—SIZE AND SHAPE OF ERYTHROCYTES ON ADDITION OF DISTILLED WATER TO PLASMA.

Patient.	Tube No. (5 cc. blood in each tube).	Distilled water added, cc.	Measured mean vol. of erythrocyte (A), cubic microns.	Measured diameter, microns.	Calculated thickness, microns.	Calculated mean erythrocyte volume from measured diameter (C), microns.	Volume-thickness index, A/C.	Hemolysis.
Normal	1	0	86	7.6	1.90	86	1.00	0
	2	1	98	7.4	2.30	79	1.24	0
	3	2	110	7.7	2.35	89	1.24	0
	4	3	129	7.2	3.15	73	1.77	0
	5	4	141	7.3	3.40	76	1.86	+
Mild congenital hemolytic jaundice	1	0	87	7.2	2.20	73	1.19	0
	2	1	99	7.0	2.60	68	1.46	0
	3	2	124	7.0	3.30	68	1.81	0
	4	3	137	6.9	3.50	65	2.11	+
Severe congenital hemolytic jaundice	1	0	72	6.1	2.75	45	1.60	0
	2	1	86	6.1	2.95	45	1.91	0
	3	2	100	6.1	3.40	45	2.22	+

The amount of dilution necessary to produce hemolysis varied with the degree of spherocytosis and so depended directly on the shape of the cell. In the severe case with a high volume-thickness index, and so a marked tendency to a globular form, very little dilution was possible before hemolysis began. The cells in this

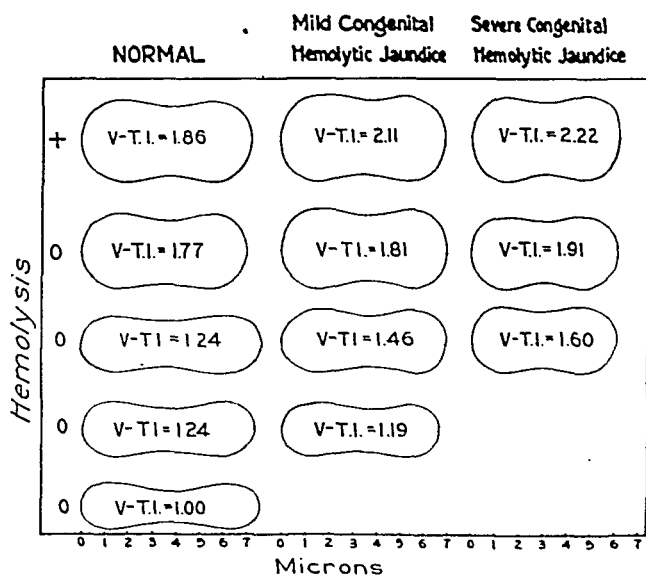


FIG. 4.—Changes in the shape and measurements of the mean erythrocyte in congenital hemolytic jaundice as contrasted with the normal erythrocyte on the addition of varying amounts of distilled water to the plasma (Table 3).

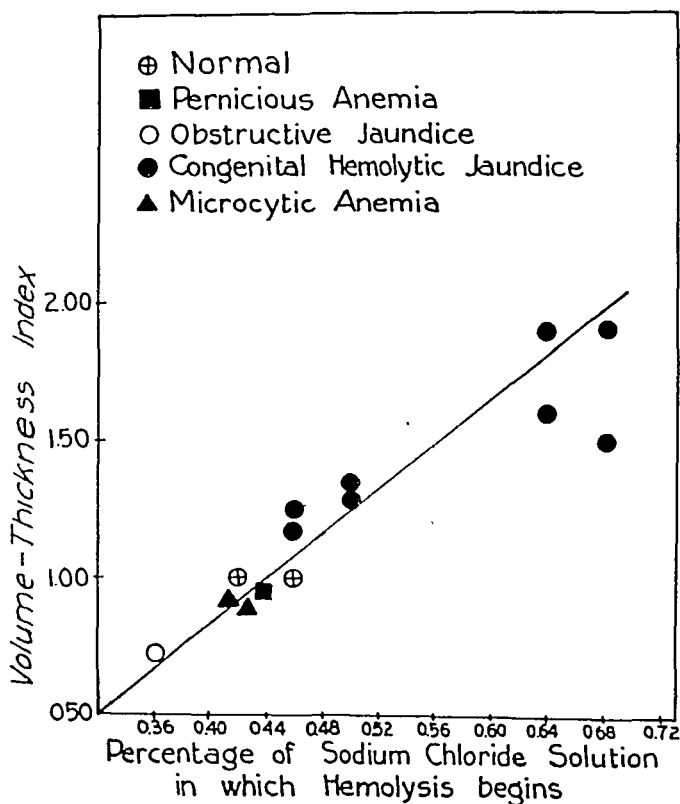


FIG. 5.—The relationship of the point of initial hemolysis of the erythrocytes to the volume-thickness index of the mean erythrocyte.

disease may be regarded as nearer the hemolysis point by reason of their shape.

It is apparent from these results that the point at which hemolysis begins in hypotonic saline solutions should be predictable from the volume-thickness index and likewise the tending to globular form from the minimal resistance. I have charted a group of cases of congenital hemolytic jaundice in Fig. 5, in comparison with obstructive jaundice and other types of anemia. There is a close relationship between the point of initial hemolysis and the volume-thickness index. In obstructive jaundice the diameter of the mean cell is increased (Fig. 1), without change in volume, so the thickness and volume-thickness index are less than normal. In such a blood the resistance is increased. If the diameter and thickness are equally increased as in pernicious anemia or equally decreased as in simple microcytic anemia (Fig. 1), the volume-thickness index and consequently the resistance are normal.

Conclusions. The erythrocytes in congenital hemolytic jaundice constantly exhibit spherocytosis, best shown by the increased volume-thickness index.

The diameter of the red cell in this condition is always less than normal; the volume is variable.

When placed in hypotonic salt solutions, normal erythrocytes become progressively more globular with little change in diameter as the solution is made more hypotonic.

There is a direct relation between the volume-thickness index and the fragility of red cells.

In congenital hemolytic jaundice, the erythrocytes have at the beginning one of the shapes through which a normal cell must pass when placed in successive dilutions of hypotonic salt solution, and so may be regarded as nearer the hemolysis point.

The one fundamental variation from normal in congenital hemolytic icterus is the microspherocytosis. The anemia, jaundice, splenomegaly, reticulocytosis and increased fragility are all secondary to the globular form of the erythrocyte.

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THE VALUE OF THE BLOOD SEDIMENTATION TEST IN THE ROUTINE MEDICAL EXAMINATION OF ADOLESCENTS AND IN CERTAIN OF THEIR DISEASES.

By J. ROSWELL GALLAGHER, M.D.,
SCHOOL PHYSICIAN, THE HILL SCHOOL,
POTTSTOWN, PENNA.

SINCE the introduction of the blood sedimentation test by Fahraeus⁵ in 1918 its value as an index of the presence of a disease process has gradually become more widely appreciated, and its part in the routine examination of patients in gynecologic⁶ and tuberculosis² clinics become generally accepted, but the employment of this diagnostic aid is not general in routine health examinations. Schattenberg⁸ has advocated its use in public health and preventive medicine as an aid in detecting obscure disease and Cutler³ has emphasized its use in the practice of general medicine. The yearly health examination of school children is certainly a public health enterprise which should be encouraged, but the difficulties which attend such a procedure are obvious; no matter how meticulous and competent the examiner, pathologic conditions may easily be overlooked. In an effort to eliminate such errors, the tuberculin test and Roentgen ray examination of the chest have been added by some health officials to the physical examination. As a possible further diagnostic aid in the yearly health examination of preparatory school boys, we began evaluation of the routine use of the blood sedimentation test in 1932. It was also employed during the course of certain diseases among those boys, to ascertain what changes take place during those illnesses in that age group, and of what significance or value the knowledge of such changes might be.

Method. Beginning in the fall of 1932, each boy presenting himself for his medical examination received a blood sedimentation test. In 1933 about $\frac{2}{3}$ of the examinees were tested both by the Cutler¹ and the Wintrobe⁹ method. We have found it convenient and satisfactory to report the readings of these tests at $\frac{1}{2}$ and 1 hour after they were set up; in somewhat less than half the cases, readings were also made at the end of 2 hours and at the end of 18 hours. These examinations were made during the fall term of each school year and the boys were under medical supervision during the remaining months of those years. In general the group might be presumed to be especially healthy since its members were all from homes where proper hygiene and medical supervision had always been available. Our opportunity of observing the boys during subsequent months further justifies the assumption that these boys were normal. Cutler¹ has considered that the normal rates at 1 hour for male adults range between 2 and 8 mm., with the average falling between 3 and 4 mm.; in female adults the range is from 2 to 10 mm., with the average between 5 and 6 mm. Wintrobe¹⁰ has found the range at 1 hour for males and females to be from 0 to 9 mm. and from 0 to 20 mm. respectively, and that 86% of normal males fall in range of 0 to 6.5 mm.

In addition to the tests made on presumably normal boys, other tests were made during certain acute febrile illnesses for the purpose of determining to what degree the sedimentation rate might have been affected. It was also hoped that the test might prove to be of aid in determining the subsidence of the pathologic process in such a disease as bronchopneumonia, in which there is a prolonged convalescence and the time at which normal activity may be resumed is always difficult to determine. The value of this test in following the course of rheumatic fever has been reported by other writers.⁴

RESULTS. In Table 1 and 2 will be found the readings of the blood sedimentation rates we obtained in 685 normal boys ranging in age from 12 to 20 years. It is our experience that the most significant readings are those obtained at $\frac{1}{2}$ hr. and 1 hr., the former serving as a guide to the rapidity with which the blood achieves the latter level.

TABLE 1.—THE BLOOD SEDIMENTATION RATE IN NORMAL ADOLESCENTS. CUTLER METHOD.

Time interval.	$\frac{1}{2}$ hr.	1 hr.	2 hrs.	18 hrs.
Range	1-6	1-12	2-20	13-29
Mean	1.5	3.2	7.5	21.5
Median	1	3	7	22
Mode	1	2	6	23
Number of cases	557	557	212	212

(Values for normal adults at 1 hour, Cutler¹: males range 2-8 mm., average 3-4 mm.; females, range 2-10 mm., average 5-6 mm.)

TABLE 2.—THE BLOOD SEDIMENTATION RATE IN NORMAL ADOLESCENTS. WINTROBE METHOD.

Time interval.	$\frac{1}{2}$ hr.	1 hr.	2 hrs.	18 hrs.
Range	1-10	1-20	2-31	16-52
Mean	2.0	4.7	9.7	32
Median	2	3	9	33
Mode	1	2	3	30
Number of cases	200	200	200	200

(Values for normal adults at 1 hour, Wintrobe¹⁰: males, range 0-9 mm., females, range 0-20 mm.)

Table 3 lists the results obtained by both methods in those individuals whose rates were at the upper limit of normal; and also shows the close parallel of results by the two methods. The examination of those tables indicates that the average normal male adolescent's blood sedimentation rate is about 3 mm. during the first hour by the Cutler technique; and about $4\frac{1}{2}$ mm. by the Wintrobe technique. The normal range for the first hour is from 1 to 12 mm. by the Cutler technique and from 1 to 20 mm. by the Wintrobe technique. Of the individuals 90% had rates of 6 mm. or less in 1 hr. by the Cutler method, and 93% had rates of 10 mm. or less in 1 hr. by the Wintrobe technique. The individuals whose sedimentation rates are listed in Table 3 were carefully followed by the Medical Department but at no time was there any evidence that any of these boys was suffering from an acute or chronic dis-

ease. In these cases, and in any instances in which the sedimentation rate was abnormally accelerated, the hematocrit was determined according to the method suggested by Wintrobe⁹ in order to eliminate anemia as a factor.

TABLE 3.—THE BLOOD SEDIMENTATION RATES BY BOTH CUTLER AND WINTROBE TECHNIQUES IN NORMAL INDIVIDUALS WITH UPPER NORMAL RATES AND NO ANEMIA.

Case.	Time interval. Method.	$\frac{1}{2}$ hr.		1 hr.		2 hrs.		18 hrs.	
		C	W	C	W	C	W	C	W
R. H.	4	4	9	15	15	27	25	45
K. H.	5	7	11	19	15	30	23	47
C. A.	6	10	12	20	17	35	26	52
J. R.	5	6	11	17	18	29	28	49
E. F.	3	7	9	16	16	26	27	50

Brief notes are given below concerning the 4 individuals who were found to have an acceleration in their sedimentation rate and in whom there was evidence of lesions which could account for that condition. In Table 4 will be found the sedimentation rate readings for each of those individuals. In the case of D. B. it may be said that the greatest value of this test is found, for although the lesions were quite extensive, it is not at all difficult to imagine that in a hasty examination they might have been overlooked.

TABLE 4.—THE BLOOD SEDIMENTATION RATES IN INDIVIDUALS IN WHOM PATHOLOGIC PROCESSES WERE PRESENT.

Case.	Time interval. Method.	$\frac{1}{2}$ hr.		1 hr.		2 hrs.		18 hrs.	
		C	W	C	W	C	W	C	W
D. B. ¹	13	24	19	43	22	50	25	55
D. H. ²	5	5	10	12	18	30	23	45
R. L. ³	6	..	12
H. L. ⁴	8	17	15	40	20	48	25	52

¹ This boy said he felt well at the time of his medical examination; but recent weight loss, cough and lassitude were admitted upon further questioning. His general appearance suggested tuberculosis and careful physical examination and Roentgen ray of the lungs confirmed that impression and explained the accelerated sedimentation rate.

² This boy had an appendectomy 4 weeks previously which probably explains the acceleration of the sedimentation rate on that day.

³ This boy felt well on the day of his medical examination and no abnormalities were noted. The cause of the slight acceleration in sedimentation rate was obvious the following day, however, when he was admitted to the infirmary with cough and fever (Temp. 100). During the course of his bronchopneumonia, the sedimentation rate became further accelerated (Table 7).

⁴ The probable explanation of the acceleration in this case was history of a recent severe common cold and subsequent frequent injections of "cold" vaccine as prophylactic measure.

In a number of individuals suffering from moderately severe common colds the sedimentation rate was determined, and a small representative list of readings are given in Table 5. It will be seen that, in general, there was little acceleration in the rate. In 6 cases of mumps (Table 6) the rate was somewhat accelerated in those individuals who had the more severe infection.

TABLE 5.—THE BLOOD SEDIMENTATION RATES IN THE COMMON COLD.

Case.	Time interval.		$\frac{1}{2}$ hr.		1 hr.		2 hrs.		18 hrs.	
	Day of disease.	Method.	C	W	C	W	C	W	C	W
C. B.	6	4	3	10	20	17	36	24	45
M. D.	3	5	4	11	18	19	40	25	50
R. F.	6	5	11	8	21	14	33	23	48
R. G.	5	7	5	16	23	23	42	27	51
J. M.	4	4	11	8	19
L. M.	4	2	3	5	9	10	18	21	43
N. P.	3	3	3	7	11	16	30	26	45
G. P.	5	2	3	7	11	15	24	27	45
J. R.	3	6	10	12	24	17	37	25	..
W. W.	6	3	3	7	9	12	17	22	41

TABLE 6.—THE BLOOD SEDIMENTATION RATES IN MUMPS.

Case.	Time interval.		$\frac{1}{2}$ hr.		1 hr.		2 hrs.		18 hrs.	
	Day of disease.	Method.	C	W	C	W	C	W	C	W
R. M.	5	5	15	14	31	18	42	25	51
	11	6	15	12	25	16	33	25	48
H. M.	2	4	6	8	16	17	35	23	43
	8	3	8	11	21	17	29	22	46
W. W.	3	3	2	7	9	13	20	25	44
G. Y.	4	1	1	2	2	6	3	20	25
	9	1	1	2	2	5	10	16	25
W. Y.	2	5	8	10	19	13	22	22	44
W. Y.*	8	9	19	17	37	22	46	26	50
H. H.†	4	3	4	10	17	17	34	23	46

* Complicated by orchitis on 6th day; † bilateral orchitis only.

In a prolonged illness such as bronchopneumonia, there is a more satisfactory opportunity of observing the effect of a disease process on the sedimentation rate. In 5 cases of bronchopneumonia in adolescents the sedimentation rates are recorded. It will be seen in Table 7 that there is little increase in the rate at the onset of the disease, but that during the development of the pneumonic process the rate becomes accelerated. It is also obvious that with the onset of convalescence there is a gradual return of the sedimentation rate to normal.

We have also frequently employed this test in helping us to determine whether or not pathologic processes were present in individuals whose past history or general appearance or symptoms suggested chronic disease. In such instances the finding of a normal sedimentation rate has given us greater confidence in the advisability of expectant treatment, and in our attempts to reassure the patient.

Comment. As part of the routine medical examination of 685 preparatory school boys, about 750 blood sedimentation tests have been done either by the method of Cutler or of Wintrobe. We have found that this test gives us further assurance that no obscure pathologic processes have been overlooked. It is true that up to the present time the test has not uncovered unsuspected disease

in many instances, but it is to be remembered that we are dealing with a group whose age and advantages should make them relatively free of illness, and that should only a rare case be found, the use of the test would be justified. The value of the test in such a case as D. B. will be apparent at once to any physician who has examined a relatively large group of boys within a comparatively brief time. In addition to the routine tests which have been reported, we have frequently employed the test when the past history or general appearance of a boy has made us uncertain that there was no disease present; in those instances we have been more confident in our opinion that all was well than we could have been had such a test not been available.

TABLE 7.—THE BLOOD SEDIMENTATION RATES IN BRONCHOPNEUMONIA.

Case.	Day of disease.	W. B. C.	Time interval.	½ hr.		1 hr.	
			Method.	C	W	C	W
R. C.	2	7300	3	4	7	11
	4	6900	6	12	13	26
	8	7500	20	30	23	45
	13	7900	19	15	24	38
	22	5900	3	4	9	17
B. D.	3	6500	6	6	13	20
	5	6400	9	24	20	44
	8	7500	6	21	20	34
	15	10300	3	6	9	15
J. W.	1	6100	12	15	20	30
	5	7200	17	20	21	38
	21	8	11	12	22
R. L.	1	9200	6	..	12	..
	2	8200	6	..	16	..
	6	9600	12	..	23	..
	10	7	..	17	..
C. M.	3	6200	5	6	17	18
	8	9400	14	22	23	45
	18	6200	3	16	11	34

It should be emphasized however, that this test is only a diagnostic aid and in no way can supplant a careful physical examination and other established diagnostic procedures. The desirability of having routine tuberculin tests and chest roentgenograms is in no way affected, for it is generally known that the blood sedimentation rate is often but little influenced in incipient tuberculosis; and it is always to be remembered that this test has real limitations and is not infallible.

The value of the blood sedimentation test in the course of acute febrile illnesses in this age group is not very great, and we can see little benefit in its routine use. In such illnesses as bronchopneumonia we have found this test a definite aid, particularly in those individuals whose cough persists and whose convalescence is slow. In those patients a steady decrease in the sedimentation rate gives one assurance that the trouble is gradually subsiding; or a continued acceleration will compel one to investigate more carefully for some complication. The tables recording the rates in a small number of

adolescents suffering from mumps and common colds, indicate how little the sedimentation rate is affected by minor infections of brief duration.

It would seem that the number of normal boys tested is sufficiently large to allow one to determine tentatively the normal range of the blood sedimentation rate in adolescents, and we have adopted the policy of carefully reëxamining and following up boys whose rate is 10 mm. or more by the Cutler technique in 1 hr. or 15 mm. or more by the Wintrobe method. The sedimentation rates of normal adolescents were found similar to those of normal adults. The question as to which of the two methods is more suitable in group testing is difficult to answer. The Cutler tube is somewhat simpler to fill, and in our experience less subject to error when not carefully cleaned; but the Wintrobe tube has the very definite advantage of permitting a subsequent determination of the hematocrit and the consequent elimination of anemia as a factor in an accelerated rate.

Summary. 1. Blood sedimentation rates in 685 normal adolescents are recorded.

2. The blood sedimentation rates occurring in the common cold, mumps and bronchopneumonia of adolescents are reported.

3. The value of the sedimentation test as a prognostic aid in such prolonged illnesses as bronchopneumonia is commented upon.

4. The desirability of including this diagnostic aid as part of the routine medical examination in a program of preventive medicine is suggested.

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METEOROLOGIC EFFECTS ON THE SEDIMENTATION RATE OF ERYTHROCYTES.

By EMIL T. HOVERSON, M.A., M.D.,
KANKAKEE, ILLINOIS,

WILLIAM F. PETERSEN, M.D.,
CHICAGO, ILLINOIS.

(From the Kankakee State Hospital and the Department of Pathology, University of Illinois, College of Medicine.)

SINCE Fahraeus¹ reintroduced the erythrocyte sedimentation test, it has been given importance as a part of the diagnostic armamentarium in many parts of the world, especially in Europe, from

which continent most of the earlier reports as to its uses originated. More recently, however American writers have discussed it with the frequency formerly encountered chiefly abroad. Although a general agreement exists² as to the functioning of the test, in that it is commonly conceded that a rapid sedimentation rate indicates an acute infection and a decreasing one connotes improvement, yet many investigators are not in accord with these views. Thus, Pinner³ and his coworkers showed that there was no correlation between the clinical picture of tuberculosis and the sedimentation rate, and he also noted that there occurred rather wide variations from day to day in "normal" individuals.

That these daily variations should occur and be noted in normal persons appears significant in that it leads one to believe that it is on the basis of such variations that disagreement occurs between various observers who were dealing with certain pathologic conditions, and who neglected to account for variations which might occur independent of any pathology.

The writer feels that, as a result of the observations to be described in this paper, it will be found that the basis of the variations in the sedimentation rate may be explained by the changes that are produced on "normal" or "abnormal" individuals by meteorologic conditions, rather than by the inroads of disease.

Although the exact mechanism of the sedimentation test is not known, many theories have been advanced. (As far as is known) it is now believed that the fibrinogen content of the blood is one of the most important factors.⁴ Recently Freeman⁵ noted a correlation between the carbon-dioxid content of the venous blood and the settling rate of erythrocytes. Hence there may be one or several yet unknown factors that determine the rate, and we make here no attempt to postulate the cause for the settling. We do believe that variations in the individual rates depend largely on environmental and meteorologic conditions.

During the course of the past 6 years, one of us (W. F. P.)⁶ has worked out the detailed physiologic and pathologic changes that are associated with meteorologic alterations, and also has demonstrated the close reflection of the shifting cyclonic fronts in the adaptive mechanism of the mammalian organism. Thus pressor episodes, falling carbon-dioxid and increasing blood pH, localized or general anoxemia, alternates with periods when the diastolic blood pressure falls, the carbon-dioxid content increases, the blood pH decreases, basal metabolism, and oxidation increases. The first phase is termed the ARS phase, and the latter COD phase. The ARS phase coincides with the infall of polar air (but may at times occur at periods of unusually high temperature and humidity). The COD phase usually is coincident with the passage of a tropical front, *i. e.*, with the cyclonic period of low barometric pressure. Not only does this rhythm (ARS and COD phase changes) influence

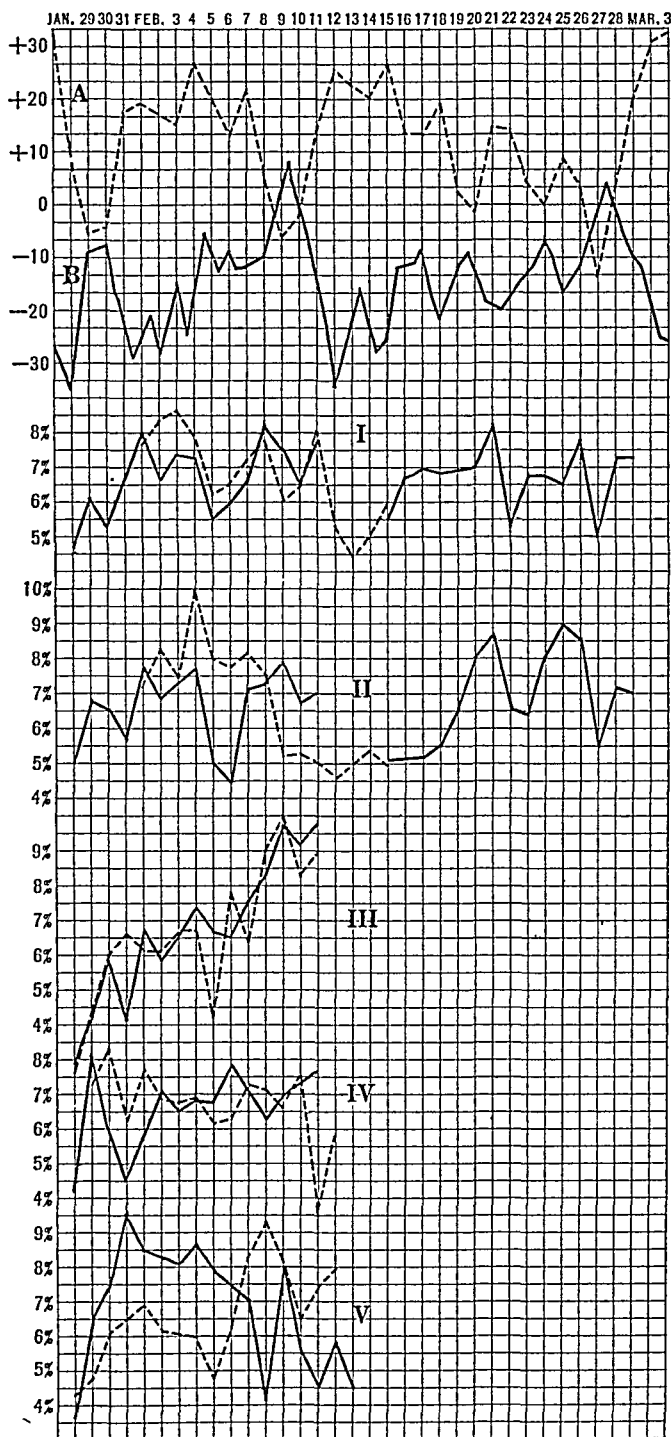
every physiologic process but it is naturally reflected to a greater extent in the individual who is poorly buffered, or in whom some organic dysfunction exists (migraine, epilepsy, eclampsia, psychosis, etc.).

Among the physiologic alterations, changes have been described for the leukocytes, the fibrin, platelets, corpuscular resistance, and so on. Now, if meteorologic conditions are able to bring about changes which may be measured by blood chemistry methods, then these same changes ought to influence the erythrocyte settling rate.

Methods and Observations.—Because of the availability of material, the determinations were made on male patients classified as general paralysis. There were two exceptions to this. Patient 1 had a 4+ blood Wassermann and Kahn test only, and Patient 12 had negative tests for syphilis. The month of February was selected for this study because of the numerous well-marked meteorologic changes which commonly occur during this month. All the determinations were carried out by the writers, under uniform conditions, 1 hour after breakfast (which was always of essentially the same ingredients). The Linzenmeier method was used in all cases in order to report on one method only. In each tube were placed 0.2 cc. of a 2% sodium citrate solution, and 1 0.8 cc. of blood, and these were mixed by inverting the tube 3 times. The time in minutes for the erythrocyte column to reach the 0.18 mark was recorded.

Other methods, namely, the Westergreen and the Cutler, are carried out by measuring the length of the plasma column after the blood has been in the tube for 1 hour. This differs from the Linzenmeier method, but the different procedure in determination has no appreciable effect on the final results. Thus it was stated by Greisheimer⁷ that the average sedimentation for the three methods in 1 hour in normal subjects appears to be reasonably concordant, although the differences between the means for the three methods were significant statistically. She also stated that the "dispersals in individual cases about the lines of average relationships although not studied in detail are clearly greater than those ascribable to error inherent in the technic." Thus it was reasoned, that if variations appeared in the Linzenmeier method, these same variations would appear in other methods.

It seems that the results do not depend upon the method used, and hence the disagreements noted among various authors cannot be due to the different methods. Even using the same method, variations occur in normal persons, and although this has been noted by several, no explanation has been advanced. It is quite probable that the issue has been clouded in that the attention has been focused on the effect of diseases, and not upon other factors extraneous to the malady which might independently affect the rate. One might almost sum it up by saying that if a person has a certain disease, then he ought to show a decreased or an increased rate, depending upon the type of the malady.



The sedimentation rate of erythrocytes: An explanation for daily variations.

The period of study extends from January 28, 1934 to March 1, 1934, inclusive and comprises determinations made on 12 patients. In each case 15 determinations were made at daily intervals whenever possible. The patients were so arranged that some one was under observation all the time.

The following table shows the data for the Patients 1, 3, 4, 6, respectively;

TABLE 1.—SEDIMENTATION RATES (IN MINUTES) IN 4 PATIENTS.

Date.	Pt. 1.	Pt. 4.	Date.	Pt. 3.	Pt. 6.
Jan. 28	55	206	Feb. 15	281	194
29	72	291	16	341	196
30	63	271	17	358	193
31	79	237	18	344	208
Feb. 1	95	325	19	345	238
2	78	287	20	357	303
3	89	310	21	418	330
4	87	320	22	262	250
5	65	209	23	342	242
6	71	185	24	341	310
7	75	304	25	332	348
8	98	303	26	394	328
9	9	339	27	240	207
10	74	278	28	375	276
11	94	300	Mar. 1	371	254

In order to obtain similar graphs for each patient, the percentage variation from day to day was determined. Thus for the 15 determinations in Patient 1 a total of 1184 minutes were required. On January 28, the first determination took 55 minutes, or 4.6% of the total 1184 minutes.

In the accompanying graph the percentage variations of the sedimentation rates are compared with the meteorologic conditions present at the time of the determination. Thus the graph lettered "A" shows the daily minimal variations in the temperature, while that lettered "B" indicates the barometric variations. The remaining graphs numbered from I to V were obtained by placing the 12 patients into 5 groups, the patients in each group showing a similar graph. The individual patients are identified according to the character of the line designating the changes:

Graph I. Pt. 1 ——— Pt. 2 ——— Pt. 3 ———. Graph II. Pt. 4 ——— Pt. 5 ——— Pt. 6 ———. Graph III. Pt. 7 ——— Pt. 8 ———. Graph IV. Pt. 9 ——— Pt. 10 ———. Graph V. Pt. 11 ——— Pt. 12 ———.

In considering the meteorologic conditions present in the period January 27 to March 2, 1934 it is seen that there occurred 9 distinct disturbances. (This is not at all uncommon for February and constitutes one of the reasons that the work was carried out at this time of the year.)

Of the 9 changes, 5 were designated as polar fronts and the remaining 4 as tropical fronts. The changes occurred respectively as follows:

January 28, tropical; January 29, polar; January 31 to February 3, tropical; February 9, polar; February 14, tropical; February 20, polar; February 21, tropical; and February 27, polar.

If the postulate is correct that daily changes in the rate of sedimentation are determined by the response of the organism to weather changes, then definite changes should occur on the dates mentioned above. An examination of the percentage variations in each patient's record discloses that usually definite changes did occur just as would be expected. (In the case of Patients 7 and 8 the effect was cumulative.) Thus, the first 7 determinations were made on January 28 and all have increased rates when compared with the following days. The next day, January 29, the barometer rose and the temperature fell, and all (then 8) of the patients showed relatively slower sedimentation rates. A longer time was required to reach the 0.18 mark.

The changes were rather indefinite on January 30 for of the 8, 3 patients showed a small increased sedimentation rate over the previous day, while 5 showed greater time. The tropical front occurs on the 31st and on that date the time for reaching the 0.18 mark should be shorter. Four out of the 7 showed this change. The same barometric conditions prevailed for the next 3 days. On the first of February, 6 of 9 patients had quicker rates, and on the 2d, 5 were slightly increased, and 5 slightly decreased, the variations being less than 1%. The same conditions existed with practically no change on February 3d.

It appears that the effect is cumulative, because on February 5 all 10 patients had a shorter time to reach the 18 m. mark. The next period of stimulation, or change, occurs on February 9. Therefore changes in the rate ought to occur on February 9 to 10. This is found to have been the case in every particular. This apparent change, occurring at tropical and polar fronts seems to be observable in all cases (it is at these periods when stimulation and changes occur).

Only 2 patients were under observation from February 15 to March 1. The correlation in these instances is self-evident.

This work could have been carried out for an indefinite length of time, but as a correlation was observed and the reasons for it were known, prolonging the observations could have no greater value.

In certain cases, namely Patients 3 and 6, it seems that the rate, whether fast or slow, is determined by the character of the change, whether it is polar or tropical. This is true in general for all cases. However, all that is expected is that the rate should show some change following a cyclonic storm, and that it should tend to the average rate for that individual afterward. Consulting the charts, it is seen that all patients except the two in whom the cumulative effect was observed, tend to group themselves about an average

percentage; thus the average percentage for any case would be 6.6%. If a line is drawn from the 6.6% on the left-hand side of the chart, this is readily seen. In order to clarify and simplify the charts, this line has been omitted.

It must be remembered that the period discussed is but a small fraction of a year, as well as being a part of a season, and that seasonal changes in bodily functions occur. Hence, the accumulative effects may be due to season, and will show an increase in the rate in the following season. Since the interest lies not primarily in seasonal changes, but instead in daily variations in the individual, this work was discontinued at this time.

Conclusions. 1. There occurs wide daily variations in the erythrocyte sedimentation rate, and at times the daily variation is as much as 100%.

2. In general paresis, the rate of settling is slower than in "normal" individuals.

3. There is a correlation between the daily variations of the sedimentation time, and the meteorologic changes.

4. It is believed that these meteorologic changes account for daily variations in the rate of settling.

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YEAST OR VITAMIN B₂ AS "EXTRINSIC FACTOR" IN TREATMENT OF PERNICIOUS ANEMIA.

BY H. C. A. LASSEN,

RESIDENT PHYSICIAN, DEP. III (MEDICAL), KOMMUNEHOSPITAL,

AND

H. KRIEGER LASSEN,

ASSOCIATE ASSISTANT, UNIVERSITY INSTITUTE OF HYGIENE,
COPENHAGEN, DENMARK.

ACCORDING to the studies on the pathogenesis of pernicious anemia published by Castle and associates,^{1,2,3} in 1929 and 1930, the antianemic principle is formed through interaction of an intrinsic factor present in normal gastric secretion, but absent in pernicious anemia, and an extrinsic factor present in certain food articles. In 1932, Strauss and Castle⁴ tentatively identified the extrinsic

factor with the thermostabile component of the vitamin B complex (B_2). The authors were unable to demonstrate any antianemic effect when 12 gm. of autolyzed yeast was given daily to patients with typical pernicious anemia, whereas there was a strong reticulocyte response when the same dose of yeast or the double dose of autoclaved yeast, as well as an 80% alcoholic extract of the preparation was given after incubation at 37° C. with 150 cc. of normal gastric juice. The yeast preparation used in these experiments was the commercial product "Vegex" which is stated to be "made from fresh washed brewer's yeast by autolysis with salt solution." Exact details of the manufacturing process of this commercial product are not given and are probably not available.

From the results obtained in these experiments Strauss and Castle conclude that the extrinsic factor "may now be defined as a substance closely related to vitamin B_2 , if not vitamin B_2 itself." This suggestion of Strauss and Castle has in recent years been much cited in the American literature, though as yet no confirmation of this suggestion has been produced and the hitherto published experiments by other authors go against it.*

Wills and Naish⁵ use the white of hen's egg for B_2 preparation (it is stated to contain a good deal of B_2 and no B_1). Daily administration of 40 to 80 "rat doses" of this preparation alone or incubated for 2 hours at 37° C. with 150 cc. of normal gastric juice proved unable to influence the regeneration of red blood cells in typical pernicious anemia. This experiment may, however, be said not to be conclusive, since the patient was not subsequently studied with a combination of gastric juice and extrinsic factor of known activity.

In 1933, Wills,⁶ studying tropical macrocytic anemia, a condition in which the intrinsic factor is assumed to be present, presents a series of careful observations on the nature of the hemopoietic factor in "Marmite" (a substance said to be similar to "Vegex"). In these experiments the B_2 content of the yeast preparations used was checked and dosage administered accordingly. Wills found the following preparations inactive in tropical macrocytic anemia: dried distiller's yeast, aqueous extracts of brewer's yeast, the acid clay vitamin B preparation of Jansen and egg white. In sharp contrast to this, maximal or marked reticulocyte response was obtained after ingestion of several different preparations of unflavored "Marmite:" the crude commercial product itself, acid as well as alkaline aqueous extracts and 80% alcoholic extract of "Marmite" (the residue was inactive) and autoclaved "Marmite" (5 hours, 120° C.). From these observations Wills concludes that the extrinsic factor is not identical with vitamin B_2 . She consequently turns

* Dr. Castle, to whom this manuscript has been shown, writes that he is fully prepared to relinquish the suggestion that vitamin B_2 is the extrinsic factor and points out the difference between Vegex or Marmite and the preparations used here.

her attention to the nature of "Marmite" as distinct from other yeast preparations. Regarding the process of manufacture of "Marmite," Wills offers the same data as advanced by Strauss and Castle concerning "Vegex," and, aware of the discrepancy between the negative results obtained with whole yeast and watery yeast extracts and the positive results with "Marmite," she suggests the possibility of the extrinsic factor in "Marmite" being some unknown protein breakdown product in the commercial preparation.

In spite of the evidence cited above, which in our opinion strongly suggests that in the tropical macrocytic condition the exogenous factor is not identical with vitamin B₂, it has been widely assumed that this vitamin plays a rôle as extrinsic factor in true Addisonian pernicious anemia.

In the studies presented in this paper our chief object has been to ascertain the possible rôle of vitamin B₂ as exogenous factor in classical pernicious anemia.

I. MATERIAL. The more important findings in the 8 cases of typical pernicious anemia on which our studies are based are tabulated below:

SURVEY OF CLINICAL AND HEMATOLOGIC FINDINGS IN PATIENTS PRIOR TO TREATMENT WITH YEAST.

Patient No.	1.	2.	3.	4.	5.	6.	7.	8.
Sex	M	M	F	F	M	F	F	M
Age	50	54	51	77	48	56	39	50
Glossitis	+	+	(+)	+	0	+	+	+
Achylia	+	+	+	+	+	+	+	+
Paresthesias	+	0	+	+	0	0	+	+
Myelit. signs	+	+	+	0	0	0	+	0
R.B.C. (millions)	2.0-1.7	1.6	2.2-1.7	2.2-1.5	1.3-1.8	2.0-1.6	3.4-2.7	1.2-1.0
Hemoglobin %	57-52	46	53-40	50-39	30-41	49-44	73-64	35-29
Color index	1.4-1.5	1.4	1.2-1.2	1.1-1.3	1.2-1.1	1.2-1.4	1.1-1.2	1.5-1.5
Plasma color	12	16	7	5	19	7	..	13
Complication	Spondylitis	Diabetes mellit.	Pyuria (B. coli)	Bronchiect.	0	0	Pyuria (B. coli)	Pyuria (B. coli)

Two figures in a column for the same feature indicate the respective values on admission of the patient and at institution of the treatment with yeast alone or with yeast + gastric juice. The plasma color values refer to the findings on admission of the patients.

II. YEAST PREPARATIONS. In the experiments 4 different yeast preparations were used:

1. *Autolyzed Viscid Brewer's Yeast (Top Yeast)*. Fresh, pressed top yeast containing 25% dry substance is autolyzed for 24 hours at 37° C. In the first experiment the patient was given 12 gm. of this preparation, a brown viscid fluid, daily—similar to Castle's dosage—and 20 gm. a day in the next experiment.

Vitamin B₂ content: 2.5 curative rat doses per 1 gm. (about 30 doses in 12 gm., and 50 doses in 20 gm.).

Vitamin B₁ content: about twice as much per weight unit.

2. *Brewer's Yeast Extract*. Fresh, pressed brewer's yeast containing about 25% dry substance is washed repeatedly, boiling water added and the mixture heated to the boiling point whereafter heating is discontinued. Then filtered through paper and Büchner's funnel and evaporated so that 1 cc. of the extract contains the same amount of dry substance as 2 gm. of the original material. The dosage of this preparation was 40 cc. daily.

Vitamin B₂ content: about 18 curative rat doses per 1 cc. (about 700 doses in 40 cc.).

Vitamin B₁ content: about twice as much.

3. *Distiller's Yeast Extract (Autoclaved for 1 Hour at 120° C. at a Pressure of 2.5 Atmospheres)*. Fresh, pressed distiller's yeast with 25% dry substance is submitted to the same procedure as preparation No. 2 and evaporated so that 1 cc. corresponds to 4 gm. dry yeast. After this autoclaving for 1 hour at 120° C. The preparation was given in doses of 20 to 30 cc. daily.

Vitamin B₂ content: about 30 curative rat doses per 1 cc., i. e., 600 to 900 rat doses in 20 to 30 cc.

Vitamin B₁ content: only a trace.

4. *Distiller's Yeast Extract (Autoclaved for 5 Hours at 120° C., pressure of 2.5 Atmospheres)*. Same method of preparation as for No. 3, but autoclaved for 5 hours. Vitamin B₂ content: about 10 curative rat doses per 1 cc. Daily dose: 20 to 30 cc., corresponding to about 200 to 300 curative doses. This preparation contains no vitamin B₁.

The preparations were assayed on rats as follows: Young male rats, aged 3 weeks, are kept on a vitamin B-free diet until the weight curve begins to fall. Then the rats are given an addition of the B₁ fraction in sufficient doses (standardized preparation), until the weight curve begins to fall anew; after this the rats are given the yeast preparation which is to be assayed for B₂—daily doses by weight.

One curative rat dose means the amount (by weight) of the assayed yeast preparation that is required as a daily dose in order to give an average weekly weight increase of about 8 gm. per test animal.

III. EXPERIMENTAL TECHNIQUE. The gastric juice is obtained from fasting normal adults (medical students) by aspiration of the stomach contents after injection of histamin in doses from 0.5 to 1 mg. The amount of normal gastric juice employed in each dose has been, as a rule, the amount which the "donor" was able to produce; so, naturally, it has been subject to some variation. Nearly always, however, the dose of gastric juice has been over 50 cc., and usually between 100 and 200 cc., a quite sufficient amount, according to Castle's findings. As soon as the gastric juice is withdrawn, it is mixed with the measured dose of yeast extract, already heated to 37° C., and the mixture is incubated at 37° C. We have not determined the hydrogen-ion concentration in these mixtures; they have nearly always been slightly acid on Congo paper, and always acid on litmus paper. Thus the reaction was always within the limits for interaction between the "intrinsic factor" and the "extrinsic factor" (Castle, Townsend and Heath³) and usually near the hydrogen-ion concentration which is considered optimal for extraction of vitamin B₂.

The incubation time for the mixture of gastric juice and yeast preparation has always been the same throughout the individual experiment; otherwise it has been varied from 1 to 1½ hours up to 24 hours.

The patients were given the mixture in the morning, fasting or a few hours after a light morning meal of tea and toast. In some cases the mixture was given without any addition; most often, however, there was added a little dark beer to camouflage the looks and the taste.

IV. EXPERIMENTS. CASE 1 (Table 1).—It is evident that this patient was regressing rapidly during the first two periods of treat-

ment, for it does not seem reasonable to attach any particular importance to the very slight increase in the reticulocyte value, hemoglobin percentage and red cell count as observed at the transition from the first to the second period.

TABLE 1.—RESULTS OF TREATMENT IN CASE 1.

Days.		Retics., %	Hb., %	R.B.C., millions.	Days.		Retics., %	Hb., %	R.B.C., millions.
1	Period I	...	57	2.0	17	.	1.2	44	1.8
5	Period II	0.9			18	.	1.1		
6	.	0.7	52	1.7	19	.	1.0		
7	.	0.6			20	.	0.7		
8	.	0.1	50	1.7	21	.	0.5	45	1.7
10	.	0.5			24	.	0.4	39	1.3
11	.	0.5			25	.	0.7		
12	.	0.6			26	.	0.8		
13	.	0.4	42	1.5	27	Period III	0.6	41	1.4
14	.	0.6			45	63	3.5
15	.	1.5							

Period I (from 5th to 15th day): prep. No. 4, 20 cc. daily—no gastric juice.

Period II (from 17th to 26th day): prep. No. 1, 12 gm. daily + normal gastric juice (150 to 280 cc.), incubated for 2 hours at 37° C.

Period III (from 27th day): large doses of active preparation from pig stomach (ventriculin).

Results. B₁-free distiller's yeast extract given in a daily dose containing about 200 effective rat doses of B₂ has no antianemic effect or, at most, only a minimal effect. Twelve grams of autolyzed brewer's yeast daily (about 60 rat doses B₁ and 30 rat doses B₂) incubated for 2 hours at 37° C. with 150 to 280 cc. of normal gastric juice has no antianemic effect.

CASE 2 (Table 2).—This patient fell off so rapidly during the two periods of treatment with yeast and with yeast + gastric juice that it was not considered justifiable to extend the latter period beyond 7 days. In this case there is not even the slightest suggestion of a reticulocyte reaction.

TABLE 2.—RESULTS OF TREATMENT IN CASE 2.

Days.		Retics., %	Hb., %	R.B.C., millions.	Days.		Retics., %	Hb., %	R.B.C., millions.
1	.	0.3	46	1.6	12	.	0.7	36	1.2
2	.	0.2			13	Period II	0.5		
3	Period I	0.2			14	.	0.4		
5	.	0.1	47	1.6	15	.	0.3		
6	.	0.1			16	.	0.7	33	1.1
7	.	0.1			17	.	0.1		
8	.	0.1			19	.	0.2	31	1.1
9	.	0.4	35	1.3	47	68	3.7
10	.	0.3							

Period I (from 3d to 12th day): prep. No. 1, 20 gm. daily—no gastric juice.

Period II (from 13th to 19th day): prep. No. 1, 20 gm. daily + normal gastric juice (80 to 100 cc.), incubated for 2 hours at 37° C.

From 19th day: daily intramuscular injection of 4 cc. of campolon.

From 22d day: daily intramuscular injection of 2 cc. of campolon.

From 35th day: daily ingestion of exhepa corresponding to 500 gm. of fresh liver.

Results. Daily ingestion of 20 gm. of autolyzed brewer's yeast, containing about 100 rat doses of B₁ and 50 rat doses of B₂, has no antianemic effect whatever, regardless of whether the yeast is given alone or after incubation for 2 hours at 37° C. with 80 to 100 cc. of normal gastric juice.

Thus we have not been able to confirm the findings obtained by Strauss and Castle,⁴ although we have copied their experimental technique as closely as practicable after their data. Yet it must be admitted—and we want to stress this point—that our yeast preparation was not similar to the preparation used by these authors: As already stated they used "Vegex," a commercial product which is said to have gone through a procedure of prolonged autolysis, including addition of salt. This special process may possibly account for the discrepancy between our results and the results of Strauss and Castle. On the other hand, our findings are quite in accordance with the negative findings obtained by Wills,⁶ using ordinary dried yeast and aqueous yeast extracts in the treatment of tropical macrocytic anemia.

From the outcome of these first experiments the idea occurred to us that the divergence might be due to the possibility that our preparation No. 1 did not contain a sufficient amount of vitamin B₂. In the following experiment, therefore, we used a preparation (No. 2) with a greater B₂ content.

TABLE 3.—RESULTS OF TREATMENT IN CASE 3.

Days.		Retics., %	Hb., %	R.B.C., millions.	Days.		Retics., %	Hb., %	R.B.C., millions.
1	Period I	...	53	2.2	23	. . .	1.6		
5	. . .	0.3	48	2.0	24	. . .	1.2	45	1.7
7	. . .	0.5			26	. . .	1.1		
9	. . .	0.1			27	. . .	0.7		
12	. . .	0.1	49	1.9	28	. . .	0.3		
14	. . .	0.3			29	. . .	0.4		
16	. . .	0.1			31	. . .	0.1		
19	Period II	0.1	40	1.7	42	43	1.6
20	. . .	0.9			51	61	2.6
21	Period III	0.7							
22	. . .	1.0	42	1.7					

Period I (first 16 days): no treatment.

Period II (from 17th to 20th day): prep. No. 2, 40 cc. daily—no gastric juice.

Period III (from 21st to 31st day): prep. No. 2, 40 cc. daily + normal gastric juice (80 to 100 cc.), incubated for 1 to 1½ hours at 37° C.

From 42d day: ventriculin in sufficient doses.

CASE 3 (Table 3).—This patient was getting worse at the time treatment was instituted with a daily dose of 40 cc. of preparation No. 2 without addition of gastric juice (on the 17th day). Six to 9 days after this treatment was instituted and after 2 to 5 days of subsequent administration of preparation No. 2 + gastric juice there is a minimal increase in the reticulocyte percentage. It would

hardly be reasonable to attach any particular significance to this slight increase; most likely, it is accidental. But even if not, this increase in the reticulocyte percentage would have to be ascribed to preparation No. 2 alone and not to the combination of this preparation with gastric juice.

Results. Brewer's yeast extract containing about 1400 effective rat doses of vitamin B₁ and 700 rat doses of vitamin B₂ per daily dose has no—or merely a minimal—antianemic effect. After incubation with 80 to 100 cc. normal gastric juice for 1 to 1½ hours at 37° C. the preparation is absolutely ineffective.

After this test we went on to try yeast preparations which contained vitamin B₂ but only very little of B₁ (preparation No. 3) or no B₁ at all (preparation No. 4).

CASES 4, 5 AND 6.—These 3 patients were all given distiller's yeast extract autoclaved for 1 hour (preparation No. 3), incubated with normal gastric juice at 37° C. for 1 to 1½ hours. On subsequent treatment with liver preparation or ventriculin all 3 cases had remission; in Case 4, however, the remission was very slow and incomplete, presumably on account of the patient's age and the complicating lung lesion.

TABLE 4.—RESULTS OF TREATMENT IN CASE 4.

Days.		Retics., %	Hb., %	R.B.C., millions.	Days.		Retics., %	Hb., %	R.B.C., millions.
1	Period I	...	50	2.2	13	.	3.5	47	
7	.	0.4	39	1.5	15	.	4.5	49	2.0
					17	.	2.2	50	
9	Period II	0.7	40						
11	.	1.9	42		55	67	2.7

Period I (first 7 days): no treatment.

Period II (from 8th to 17th day): prep. No. 3, 20 cc. daily, incubated with 20 cc. of normal gastric juice.

From 17th day: ventriculin, corresponding to 300 to 400 gm. fresh pig stomach daily.

TABLE 5.—RESULTS OF TREATMENT IN CASE 5.

Days.		Retics., %	Hb., %	R.B.C., millions.	Days.		Retics., %	Hb., %	R.B.C., millions.
1	Period I	...	30	1.3	12	.	0.9		
2	.	5.0			15	.	1.9	44	1.6
					16	.	2.3		
4	Period II	3.0	41	1.8	17	.	2.1		
5	.	1.8	40		18	.	1.6	50	2.0
7	.	0.9			19	.	1.5		
8	.	1.5	40	1.5	21	.	0.3		
9	.	1.1							
10	.	0.4			22	.	0.5	55	2.1
11	.	1.0	41	1.6	36	65	2.9

Period I (first 3 days): no treatment.

Period II (from 4th to 21st day): prep. No. 3, 20 cc. daily, incubated with 80 to 180 cc. of normal gastric juice.

From 24th day: ventriculin in sufficient doses.

TABLE 6.—RESULTS OF TREATMENT IN CASE 6.

Days.		Retics., %	Hb., %	R.B.C., millions.	Days.		Retics., %	Hb., %	R.B.C., millions.
1	Period I	...	49	2.0	32	.	3.5		
4	.	0.9			33	.	3.6	45	1.7
7	.	0.9	47	2.0	34	.	3.2		
10	.	0.7			35	.	3.1		
12	.	0.3	45	1.9	37	.	2.7	49	1.9
14	.	0.4	43	1.6	38	.	2.6		
					39	.	3.0		
18	Period II	0.5	44	1.6	40	.	4.0	55	2.1
19	.	1.1			41	.	3.7		
20	.	0.8			42	.	1.5		
21	.	0.2	43	1.5	44	.	1.4	60	2.4
23	.	0.7			45	.	1.4		
24	.	1.9			46	.	0.5		
25	.	1.8			47	.	0.8	61	2.6
26	.	1.6	43	1.6	48	.	0.6		
27	.	1.7			49	.	0.5		
28	.	2.1							
30	.	3.0	44	1.5	51	.	0.3	61	2.5
31	.	2.9			55	72	3.0

Period I (first 17 days): no treatment.

Period II (from 18th to 50th day): prep. No. 3, 20 cc. daily, incubated with 60 to 105 cc. of normal gastric juice.

From 51st day: liver extract in sufficient doses.

In these 3 cases (Nos. 4 and 6 were in retrogression when administration of yeast extract and gastric juice was commenced) there appeared during the treatment small, though unmistakable, increases in the reticulocyte percentage, but mostly late in the treatment (Case 4, max. 4.5% after 8 days; Case 5, max. 2.3% after 13 days; Case 6, max. 4% after 23 days). There was at the same time a not inconsiderable increase in the hemoglobin percentage and the red cell count.

In these 3 cases, we think, the possibility of a spontaneous remission cannot be excluded; in Case 5 it is even highly probable that a spontaneous remission was coming on immediately before the treatment was instituted. On the other hand, these remissions might also be said to resemble the remissions observed after small and insufficient doses of liver extract. Whether some part in these remissions is to be attributed to the gastric juice, through its supposed action upon the yeast extract, must be said to be most doubtful, as the produced reactions are not essentially different with regard to magnitude from the minimal reactions observed in the first experiments after administration of yeast extract alone. But, on the other hand, it is not to be denied that there still *is* some difference. In our opinion the *course* of the reticulocyte curves in these experiments suggests that these patients were given a sub-optimal dose of antianemic effective principle.

Results. Treatment of 3 patients with a daily dose of 20 cc. of distiller's yeast extract, autoclaved for 1 hour at 120° C. and

incubated for 1 to 1½ hours at 37° C. with 20 to 180 cc. of normal gastric juice, is accompanied in all 3 cases by a slight but distinct reticulocyte reaction which is followed by an increase in the hemoglobin percentage and red cell count. The daily dose of yeast extract used in these cases contains about 600 curative rat doses of vitamin B₂ and only insignificant amounts of B₁.

If one were to maintain the idea that ordinary yeast contains an antianemic factor or a factor that is capable of antianemic effect after it has been exposed to the action of normal gastric juice, the outcome of the tests above would make it necessary also to look for some cause why the obtained remissions—that is, if they actually were “obtained”—have been incomplete (inadequate reticulocyte reactions observed in Cases 4, 5 and 6).

As in our experiments the chief purpose was to ascertain whether any antianemic properties may be attributed to vitamin B₂, the yeast extract employed in Cases 4 to 6 (preparation No. 3) must be said to be suitable, containing considerable amounts of B₂ and very little B₁. According to the works of Castle and his associates,^{1,2,3} cited above, the given doses of normal gastric juice must be regarded as sufficient, and the hydrogen-ion concentration of the mixture during the incubation was such as must reasonably be taken to promote a biochemical combination of the “intrinsic factor” in the gastric juice and the presumed “extrinsic factor” in the yeast extract—regardless of whether this “extrinsic factor” were identical with B₂—not suggested very strongly by the results given above—or some other substance present in the yeast extract.

A change in the experimental technique which conceivably might result in production of a larger amount of antianemic principle in the mixture of gastric juice and yeast extract would be a longer period for interaction between the two components. In the last two experiments, therefore, we have used preparation No. 4, which is entirely free from vitamin B₁ and rich in B₂, and we have incubated it with normal gastric juice at 37° C. respectively for 5 to 7 hours (Case 7) and 24 hours (Case 8).

CASE 7 (Table 7).—Here the hemoglobin percentage and red cell count were stationary when the treatment commenced, but at that time the red cell count was so high that the reticulocyte response to optimal liver therapy could not be expected to exceed 6 to 7%.

On comparison of the reticulocyte percentages ascertained during the treatment to the values obtained prior to the treatment, this patient, too, may perhaps be said to show an attempt, albeit very feeble, at reticulocyte reaction. The hemoglobin percentage does not increase at all, and the red cell count but very little. The slight reticulocyte increase observed in this case does not differ in magnitude from the preceding reticulocyte reactions after yeast medication alone.

TABLE 7.—RESULTS OF TREATMENT IN CASE 7.

Days.		Retics., %	Hb., %	R.B.C., millions.	Days.		Retics., %	Hb., %	R.B.C., millions.
7	Period I	...	70	3.2	31	. . .	1.2		
9	. . .	0.1			33	. . .	1.5	63	2.8
13	. . .	0.4			34	. . .	1.8		
16	63	2.6	35	. . .	1.6		
20	. . .	0.3	64	2.7	36	. . .	0.8	64	2.6
23	Period II	0.2			37	. . .	1.0		
24	. . .	0.5			38	. . .	0.9		
26	. . .	0.7	65	2.9	40	. . .	0.9	63	3.0
27	. . .	0.9			41	. . .	1.0		*
28	. . .	1.0			42	. . .	0.6		
29	. . .	1.4	65	2.8	43	. . .	0.8	62	2.9
30	. . .	1.6			65	72	3.3

Period I (first 21 days): no treatment.

Period II (from 22d to 41st day): prep. No. 4, 25 cc. daily, incubated with 70 to 140 cc. normal gastric juice.

From 43d day: treatment with ventriculin and, later, with liver extract. The retardation of the remission is due presumably to the complicating pyuria (*B. coli*).

CASE 8.—This patient was in a rather poor condition when he entered the hospital. To begin with, we had planned a foreperiod of 10 days in which the patient was to have only preparation No. 4, distiller's yeast extract autoclaved for 5 hours. After 5 days, however, in which the general condition of the patient was aggravated, we thought it would not be justified to keep on longer with this medication alone. Besides, in a previous test (Case 1) preparation No. 4 had already proved perfectly ineffective or almost so. We then went on to give the patient a mixture of preparation No. 4 and gastric juice, with a view to the possibility that this mixture might show some effect because the state of the blood in this case left plenty of room for improvement.

TABLE 8.—RESULTS OF TREATMENT IN CASE 8.

Days.		Retics., %	Hb., %	R.B.C., millions.	Days.		Retics., %	Hb., %	R.B.C., millions.
1	35	1.2	13	. . .	0.2		
2	Period I	0.1			14	. . .	0.2	28	1.1
4	. . .	0.6	30	1.0	15	. . .	0.5		
5	. . .	0.4			16	. . .	0.6		
6	. . .	0.5	29	1.0	18	Period III	1.1	30	1.3
7	. . .	0.2			19	. . .	1.7		
8	Period II	0.2			20	. . .	2.7		
9	. . .	0.5			21	. . .	2.3	28	1.1
10	. . .	0.2			22	. . .	2.4		
11	. . .	0.2	27	1.0	23	. . .	1.9	32	1.1
12	. . .	0.3			39	52	2.2

Period I (from 2d to 7th day): prep. No. 4, 20 cc. daily—no gastric juice.

Period II (from 8th to 16th day): prep. No. 4, 20 cc. daily, incubated with 100 to 170 cc. normal gastric juice.

Period III (from 17th to 22d day): injection of liver extract in doses which were assumed to be sufficient. Apparently the preparation was inactive. Therefore,

From 23d day: ventriculin in usual doses (typical remission).

Result (Cases 7 and 8).—Administration of vitamin B₁-free distiller's yeast extract (autoclaved for 5 hours at 120° C.), containing 200 to 300 effective rat doses of vitamin B₂ per daily dose, gives no demonstrable antianemic effect after incubation with normal gastric juice in sufficient doses for 5 to 7 hours and 24 hours, respectively. So the longer incubation time has not furthered the production of antianemic active principle.

Conclusions. In accordance with Wills, studying tropical macrocytic anemia, we have to conclude from the results of our tests that the extrinsic factor desired in the treatment of classical pernicious anemia is not identical with the B₂ fraction of the vitamin B complex and, probably, not with any other fraction of this vitamin. On the other hand, these studies suggest that some sorts of yeast (or yeast preparations) contain certain amounts of an antianemic principle, presumably similar to the substance demonstrated in "Vegex" or "Marmite"—that is, if the incomplete remissions observed in some of these cases are not to be regarded as spontaneous. If this active principle be actually present in ordinary yeast, it most likely is preformed or produced through the procedure of autolysis, as it was not practicable with certainty to ascertain any increase in its amount after incubation with normal gastric juice in sufficient doses for periods varying between 1 hour and 24 hours.

Yeast is thus entirely without any antianemic effect under the conditions of this study; or, "at best," it contains only insignificant amounts of antianemic factor.

Summary. Eight patients with typical pernicious anemia have been treated with various yeast preparations, given partly without additions of any kind, partly after incubation with normal gastric juice.

These yeast preparations are assayed by tests on rats as to their contents of vitamins B₁ and B₂. One preparation which contained no B₁ was found to be highly effective against experimental B₂ deficiency in rats.

The extrinsic factor searched for by Castle is not identical with vitamin B₂, nor with B₁, and presumably not with any other fraction of the vitamin B complex.

Yeast appears to be either completely without any antianemic effect, or it possibly contains minimal amounts of antianemic factor.

On addition of normal gastric juice it has not been practicable with any degree of certainty to ascertain an increase in the content of active antianemic principle.

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STUDIES ON THE EFFECT OF NARCOSIS ON THE RATE OF LOCOMOTION OF POLYMORPHONUCLEAR LEUKOCYTES IN VITRO.*†

BY HARRY LOWENBURG, JR., A.B.,

PHILADELPHIA, PA.

(From the Department of Pathology, University of Pennsylvania.)

THE experiments herein reported were designed to answer one phase of the following question: Has general anesthesia any effect on the resistance of the body to infection? The effect of anesthetics on the locomotion of leukocytes is the more immediate phase here considered.

The mobilization of leukocytes is an essential element in cellular immunity. Since mobilization is dependent upon locomotion, it follows that by altering the rate of locomotion of leukocytes anesthetics may thereby alter the cellular reaction to infection. It is obvious that in sufficient concentrations they would narcotize the cell and so inhibit locomotion. This would conceivably affect resistance to infection unfavorably. But what would lower concentrations do? They would possibly increase the motility by decreasing cell viscosity or by some other means. Bond¹ stated that leukocytes of patients under ether narcosis showed increased motility (though he did not report any actual measurements). On the other hand, Pantin² found no concentration of narcotic that increased motility of amebæ. Now increased motility in itself might tend to increase resistance to infection. Therefore, I sought any concentration of narcotic that would increase the rate of locomotion

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of polymorphonuclear neutrophils. In the following experiments chloroform was used as the type drug.

Technique. The method employed in these experiments was essentially that of McCutcheon³ as used by him in studying the normal rate of locomotion of leukocytes. A drop of blood mixed with the chloroform in the ratio of 4 parts of blood to 1 part of chloroform dilution was placed upon a carefully cleaned coverslip. The latter was then gently placed upon a similarly cleaned glass slide so that the drop would spread evenly in all directions. The preparation was then rimmed with vaselin in order to exclude air and placed in a warm box maintained at 37.5° C. Final dilutions of chloroform, ranging from M/64000 to M/125 in geometrical progression constituted the series employed.

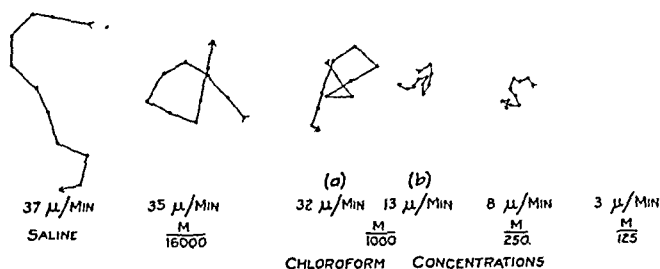


FIG. 1.—Representation of cell movements under various concentrations of chloroform for 10-minute periods.

It is important that these procedures be carried out rapidly and with as little damage to the cells as possible. Therefore, the mixing of the two solutions was accomplished by gently drawing them up into the lumen of a pipette and then gently expelling them. This procedure was repeated several times. To insure as close an approximation to physiological conditions as possible the preparation was allowed to remain in the warm box on the stage of the microscope for at least 45 minutes before observations were

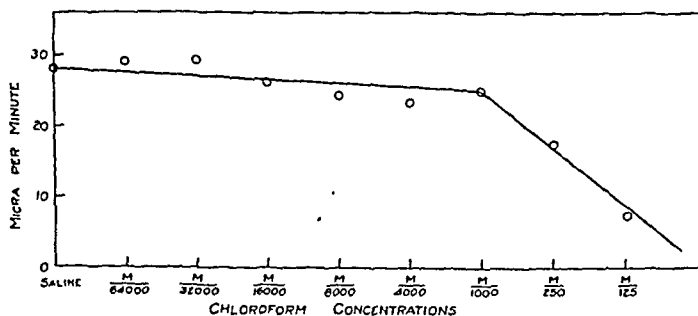


FIG. 2.—Average rate of locomotion at various concentrations.

begun. This was ample time for the cells to recover from the effects of chilling and of the manipulations so that they had once more resumed their normal movements. McCutcheon³ found that under these conditions the cells maintained normal locomotion for about 7 hours. He also found that after chilling, the cells upon regaining body temperature would resume their normal movements.⁴ Therefore, the relative complexity of the above procedures appear justifiable.

The observations were recorded by means of a Zeiss drawing ocular. The cells were observed through the high dry power of the microscope, their images being reflected onto a sheet of paper by means of the drawing ocular. The movements of each cell were observed over a period of 10 minutes, its position at the end of every minute being noted by means of a pencil-point mark in the center of its longest axis. In this manner a series of dots were obtained which when connected represented the movements of the cell over the 10-minute period. Typical results are represented in Fig. 1. Generally, not more than 3 neutrophils appear in the field, and at any one time during the experiments not more than 3 cells were followed. From 10 to 15 cells were observed in any one preparation, and these constituted one experiment.

Control determinations were made throughout the course of the experiments without the addition of chloroform. As before, the blood was diluted in the ratio of 4 parts of blood to 1 of diluent, the latter being normal saline. The blood of the same normal person was used throughout the course of the experiments.

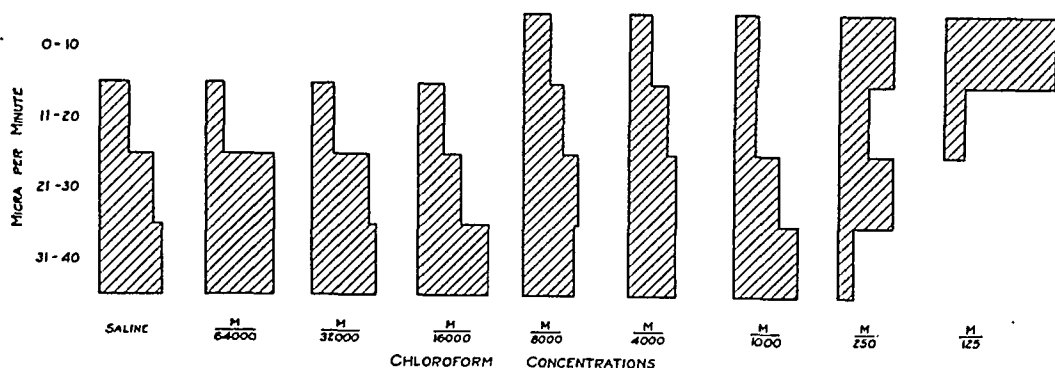


FIG. 3.—Classification of cells in percentage groups.

Results. The cells were classified according to the average rate of locomotion per minute. (Fig. 3.) They were further placed into 4 groups according to their rate over the 1-minute period, *viz.*, those cells moving from 0 to 10 micra per minute constituting the first group; 11 to 20, the second; 21 to 30, the third; and 31 to 40, the fourth. As the distribution of cells in the saline controls and in the 3 lowest concentrations of chloroform is very similar, it is suggested that in these concentrations chloroform had no effect. However, in higher concentrations there is observed an increasing shift toward a slower rate, indicating a definite and progressive effect of the chloroform in decreasing the rate of locomotion. There is no evidence that in any concentration chloroform increases the rate of locomotion.

In the control experiments of the present series an average rate of 28 micra per minute was obtained. (Fig. 2.) McCutcheon found the average rate under normal conditions and a similar technique to be 34 micra per minute. This difference was to be anticipated as the cells were subjected to more manipulations and

the blood was diluted with saline in these experiments. Fig. 2 also shows that there was no significant variance between the effect of low concentrations of chloroform on the cells and under control conditions. A sharp fall in the average rate of locomotion is noted when higher concentrations are reached.

Discussion. The results of these experiments reveal no concentration of chloroform that increases the rate of locomotion of polymorphonuclear leukocytes. Little effect of the narcotic on the cells was observed until concentrations strong enough to narcotize the cells were reached. It is interesting to note the variance in the susceptibility of the different cells to narcosis. This phenomenon is best illustrated at a chloroform concentration of M/250. It is at this concentration that we first note a decided narcotic effect. Nevertheless we still find cells moving between 31 and 40 micra per minute. It is true that the cells were well distributed among the three highest groups in the control experiments, but no cell was found to be moving at a rate greater than 40 micra per minute. Therefore, it appears obvious that all the cells are not affected equally by the chloroform. An adequate explanation of this finding is lacking. Certainly all the cells in the various groups were subjected to the same concentration of the narcotic.

The relation between the concentrations of chloroform used under the conditions of these experiments and those in the blood during surgical anesthesia is an apparent question. Several sets of figures relating to the concentration in the blood during anesthesia are available in the literature. They follow: Nicloux,⁵ 0.05% (dog); Tissot,⁶ 0.0291 to 0.0464% (dog); Buckmaster and Gardner,⁷ 0.026 to 0.05% (cat); Van Dessel,⁸ 0.023 to 0.0247% (man).

Van Dessel's figure in man is slightly lower than those occurring in animals. However, both Van Dessel⁸ and Alcock⁹ state that the differences in the concentrations between the various animals (including man) are not sufficient to vary the conclusions to be drawn from them. From these figures it is seen that during anesthesia the concentration of chloroform in the blood lies somewhere between 0.023% and 0.05%, or in molar concentrations between M/530 and M/240. There is a uniformity of opinion among Nicloux, Tissot, Buckmaster and Gardner, Van Dessel, and Alcock as to the average lethal concentration of chloroform in the blood, namely, slightly higher than a concentration of 0.07% (M/180). However, since Buckmaster and Gardner obtained lethal effects in certain cases at a concentration of 0.045 (M/260) and since the concentration in man is slightly less than that in the animal, it is likely that the actual concentration in the blood during anesthesia is less than M/300. As already pointed out, a definite slowing of the cells occurred at concentrations higher than M/1000. Therefore, it is suggested that the same phenomenon occurs during surgical anesthesia. Since the mobilization of leukocytes is an essential factor

in cellular immunity, it might follow that anesthesia diminishes this phase of the body's resistance to infection.

Summary. 1. A series of experiments have been carried out to study the effects of high and low concentrations of a narcotic (chloroform) on the rate of locomotion of polymorphonuclear leukocytes.

2. Low concentrations of the narcotic have no apparent effect on the cells under the conditions of these experiments, whereas higher concentrations inhibit their motility considerably.

3. The variance in the susceptibility of the cells to narcosis has been noted.

4. The relation between the concentration of chloroform in the blood during surgical anesthesia and those used under the conditions of these experiments has been discussed.

I am indebted to Morton McCutcheon for his help in suggesting and carrying out this problem.

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THE RELATION BETWEEN THE TOTAL RETICULOCYTE PRODUCTION AND THE DEGREE OF BONE MARROW INVOLVEMENT IN PERNICIOUS ANEMIA.*

BY FRANK H. BETHELL,

INSTRUCTOR, DEPARTMENT OF MEDICINE, AND RESEARCH ASSISTANT, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICH.

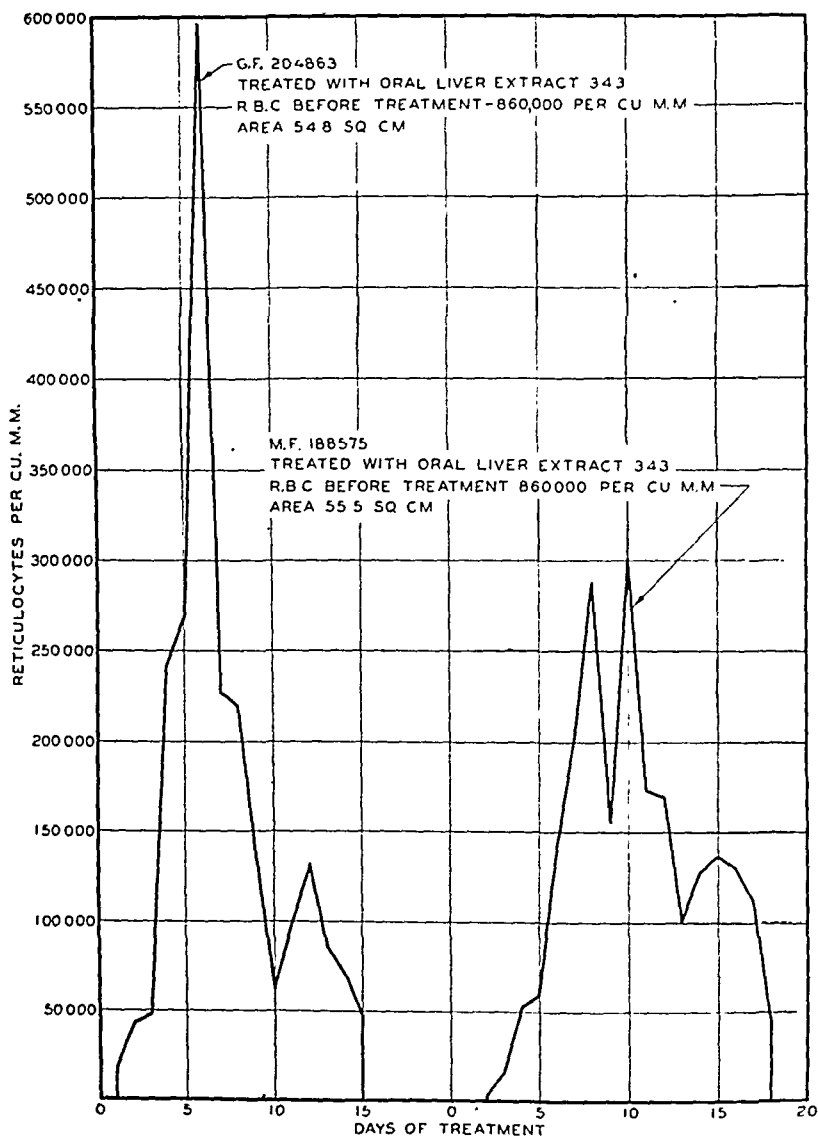
(From the Thomas Henry Simpson Memorial Institute for Medical Research, Cyrus C. Sturgis, Director, University of Michigan.)

AMONG the many observations of the effect of liver and stomach therapy upon persons suffering with pernicious anemia, probably the most striking concerns the quantitative relationship between the erythrocyte level at the beginning of treatment and the subsequent increase in the percentage and absolute number of reticulocytes.

The extensive studies of Minot and his associates,^{2,3} Riddle,⁴ Bethell and Goldhamer,⁵ supported by many other observers, clearly demonstrated that the peak of the reticulocyte rise bears an inverse

* Reported to the Central Society for Clinical Research, October 27, 1933.¹

relation to the number of red blood cells per c.mm. and that when optimal amounts of potent material are administered, the maximum reticulocyte percentage is definite for any given initial red blood cell count below 3,000,000 per c.mm.



FIGS. 1 AND 2.

Patient No. 1.

Patient No. 2.

"Reticulocyte response" curves of different shape but the same area. Both patients had the same initial red blood cell count.

The entrance into the circulation of large numbers of reticulocytes is regarded as an indication of excessive bone-marrow activity, the rate of maturation being so rapid that the developing erythro-

cytes are released before they have attained full maturity. In the usual case of pernicious anemia receiving optimal doses of liver or stomach, the duration of the reticulocyte response varies between 10 and 15 days regardless of the level of the red blood cells. However, an individual will be encountered occasionally, who displays a more sustained response, the reticulocyte percentage being ele-

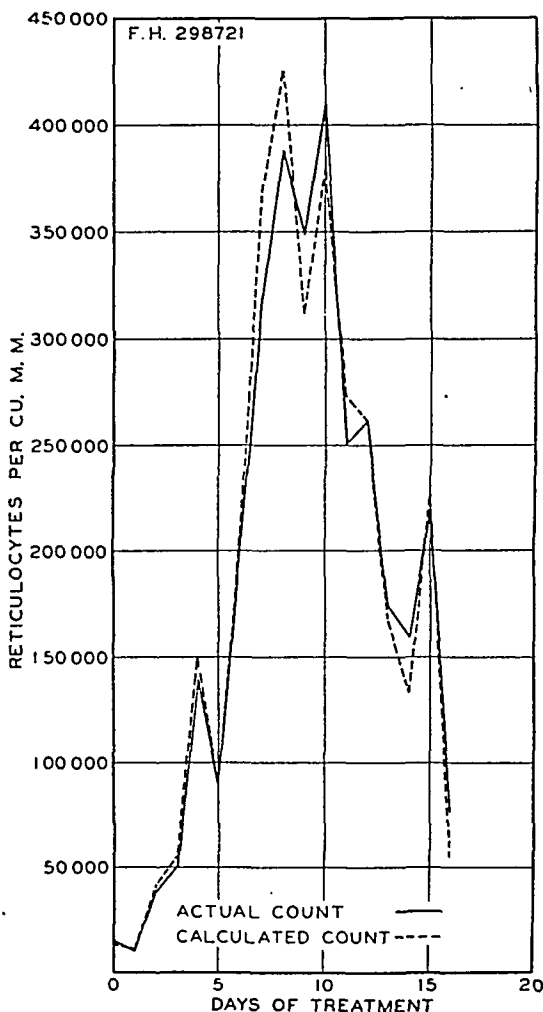


FIG. 3.—Close approximation of curves based on actual blood counts and on counts interpolated from weekly observations.

vated over a period of 20 days or longer. In such a case the maximum percentage is usually appreciably less than would have been expected on the basis of the initial red blood cell count. Furthermore, some individuals exhibit a rapid rise of the reticulocytes to a relatively high level followed by an equally precipitate decline, while others with approximately the same red blood cell count

reach a somewhat lower level and maintain it for 3 or 4 days (Figs. 1 and 2). Such variations in the type of response suggest the importance of determining a measure of the total reticulocyte production regardless of the rate or the maximum value obtained at any given time. The present study was designed to establish, if possible, the relation between the entire reticulocyte response and the initial degree of bone-marrow involvement, as evidenced

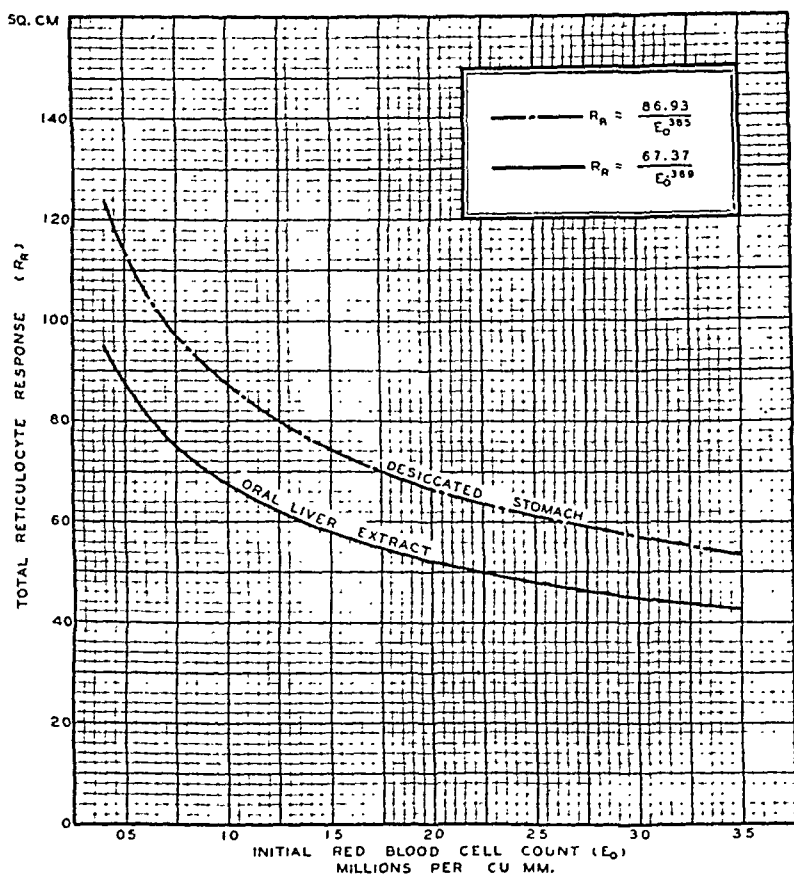


FIG. 4.—Relationship between the total plotted area in square cm. and initial red blood cell count in patients with pernicious anemia receiving liver extract orally and desiccated stomach.

by the red blood cell count at the beginning of treatment in patients who subsequently obtained satisfactory remissions induced by liver extract or desiccated stomach therapy.

Method. The patients, from whom the data under consideration were obtained, were seen at this Institute between 1927 and 1933. The diagnosis of pernicious anemia was established by clinical and laboratory criteria as well as by the subsequent response to specific anti-anemic therapy. Liver extract (343 N. N. R.) or a similar extract was administered by mouth daily in an amount derived from 600 gm. of liver, to 41 patients. Desic-

cated stomach (Ventriculin) was given in a daily dosage of 40 gm. obtained from 265 gm. of fresh stomach tissue to 33 patients. The erythrocyte determinations were made with U. S. Bureau of Standard certified pipettes and hemacytometers. The reticulocyte percentages were estimated by counting the number present in 1000 red blood cells, using cover-glass preparations supravitaly stained with brilliant cresyl blue and counter stained with Wright's stain.

It was found that a satisfactory measurement of total reticulocyte production could not be obtained by the use of percentage values. Minot and his collaborators emphasized the value of determining the absolute number of reticulocytes, but as this procedure requires practically daily red blood cell counts and has few advantages in estimating the response to treatment, it has been displaced by the study of the percentage only. For the present purpose it was necessary to have daily red blood cell counts as well as reticulocyte percentages. Since few of the cases studied offered such data a compromise was effected whereby the absolute number of reticulocytes was calculated by multiplying the daily percentage value by the erythrocyte count made on the nearest day. As red blood cell counts were made at least once a week on all patients, the value used in making the calculations was within the limit of error when compared with the actual erythrocyte level. The data given in the following tables and chart, obtained from cases on whom daily red blood cell counts were made, shows the close approximation of the results derived by calculation of the red blood cell level using weekly counts and those secured by utilizing the daily counts (Tables 1 and 2, Fig. 3).

TABLE 1.—METHOD OF CALCULATING CONCENTRATION OF RETICULOCYTES PER C.MM. AND COMPARISON OF VALUES OBTAINED BY CALCULATION AND BY ACTUAL DETERMINATION.

Days.	Red blood cells (in millions per c.mm.).	Reticulocyte percentage.	Absolute No. of reticulocytes calculated from daily red cell counts per c.mm.	Absolute No. of reticulocytes calculated from weekly red cell counts per c.mm.
1	1.60	1.6		
2	1.48	0.8	13,320	14,400 (1.60)
3	1.64	0.6	9,880	9,600 (1.60)
4	1.61	2.6	41,860	38,220 (1.47)
5	1.61	3.4	54,740	49,980 (1.47)
6	1.56	9.6	148,760	141,120 (1.47)
7	1.47	6.1	89,670	89,670 (1.47)
8	1.44	14.3	205,920	200,210 (1.47)
9	1.69	21.8	368,420	320,460 (1.47)
10	1.61	26.4	425,040	388,080 (1.47)
11	1.67	18.7	312,290	349,690 (1.87)
12	1.74	21.9	381,060	409,530 (1.87)
13	2.04	13.4	273,360	250,580 (1.87)
14	1.87	14.0	261,800	261,800 (1.87)
15	1.80	9.3	167,400	173,910 (1.87)
16	1.58	8.5	134,300	158,950 (1.87)
17	1.91	11.8	225,380	220,600 (1.87)
18	1.95	2.8	54,600	76,440 (2.73)
21	2.73			

The values to the right of the last column are those of the erythrocyte count used in making the calculation. This patient received 40 gm. of Ventriculin daily.

The concentration of reticulocytes was determined daily, using the method just described, commencing one day after the beginning of treatment and continuing until the reticulocyte percentage was within 1% of that found on the day treatment was instituted. The values were plotted on standard

graph paper, the ordinate being time represented in days, 0.2 inch (0.504 cm.) representing 1 day; the abscissa being the number of reticulocytes per c.mm., 0.2 inch (.504 cm.) representing 10,000 reticulocytes. Using the base as one side of the curve, the area of each graph was determined with a planimeter.

TABLE 2.—COMPARISON OF THE AREA OCCUPIED BY THE GRAPH OF THE DAILY RETICULOCYTE NUMERICAL CHANGES, PLOTTED ON PAPER, WHEN MADE FROM THE ACTUAL DAILY RED BLOOD CELL COUNTS AND FROM COUNTS INTERPOLATED FROM WEEKLY DETERMINATIONS.

Patient.	Initial red blood cells million per c.mm.	Area on actual count, sq. cm.	Area on calculated count, sq. cm.	Per cent error.
1. M. F.	0.86	40.9	40.7	0.5
2. I. G.	2.04	44.9	45.1	0.4
3. B. H.	1.27	30.1	30.8	2.3
4. F. H.	1.52	40.2	39.3	2.3
5. C. J.	1.91	32.8	32.7	0.3
6. G. J.	0.78	36.0	35.6	1.1
7. W. M.	0.82	92.3	95.1	3.0
8. P. S.	0.64	55.1	56.6	2.7

Maximum error 3.0%. Average error 1.58%. Patients 4 and 5 were treated with Ventriclein; the others received liver extract by mouth.

From the data obtained, formulas were constructed by which a measure of the expected total reticulocyte response can be secured from a knowledge of the initial red blood cell count.

$$\text{For liver extract by mouth} \quad R_r = \frac{67.37}{E_o .369} \text{ sq. cm.}$$

$$\text{For desiccated stomach} \quad R_r = \frac{86.93}{E_o .385} \text{ sq. cm.}$$

In which R_r is the "area of the reticulocyte response" in square centimeters and E_o the initial erythrocyte count (millions per c.mm.).

By the use of these formulas curves were prepared for the "area of the reticulocyte response" similar to those devised by Riddle⁴ and by Bethell and Goldhamer⁵ for the maximum reticulocyte percentage response in terms of the initial red blood cell level (Fig. 4).

It was found that, while the inverse relationship between the initial erythrocyte concentrations and the total production of reticulocytes is much less marked than in the case of the maximum reticulocyte percentage response, nevertheless, such a relationship does exist, and the total area of the graph is uniformly proportional to the level of the red blood cells at the beginning of treatment.

Summary and Conclusions. In an effort to estimate the comparative quantities of reticulocytes produced during the initiation of a remission in different pernicious anemia patients, the areas circumscribed by the graphs of the "reticulocyte responses" plotted on a standard paper, were measured in square centimeters.

The value so obtained for any patient is an expression of the total reticulocyte response of that patient.

There is a direct relationship between the degree of bone-marrow involvement, as evidenced by the severity of the anemia, and the summation of the reticulocyte response as represented by the area of the graph. Formulas are given which express this relationship.

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THE RELATION OF AMIDOPYRIN AND ALLIED DRUGS TO THE ETIOLOGY OF AGRANULOCYTIC ANGINA.

By HENRY JACKSON, JR., M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

(From the Thorndike Memorial Laboratory, 2d and 4th Medical Services (Harvard); the Pathological Laboratory, Boston City Hospital; the Department of Medicine and the Collis P. Huntington Memorial Hospital, Harvard University.)

A NUMBER of authors¹⁻⁶ have recently suggested that amidopyrin (pyramidon) and other drugs of similar nature which contain a masked benzene ring may be the cause of the clinical syndrome agranulocytic angina. The evidence presented in support of this hypothesis consists in the fact that one or more drugs of this class have been taken by the patient in considerable quantities for varying periods of time prior to the onset of the disease and supportive evidence is believed to be afforded by the known leukotoxic effect of benzene, together with the fact that the drugs under suspicion contain a modified benzene ring. Madison and Squier³ found, furthermore, that in 2 of their patients a brief drop in leukocyte count followed the administration of small doses of these drugs after the patients had recovered from their original attack. Hoffman, Butt and Hickey⁴ noted that "the only common factor in the 12 cases seen had been the ingestion of amidopyrine." No details are supplied as to the clinical or hematologic pictures in the cases under observation. Madison and Squier³ also note that all 6 of their cases which continued to take amidopyrin died, whereas in 8 cases in which the drug was prohibited after the onset the mortality was only 15%. The serious implications of these allegations are obvious. A general summary of the situation has recently been presented.⁷

In consideration of the etiology of any condition, several points must be constantly borne in mind. Chance alone may play havoc with our reasoning. To amidopyrin and allied drugs that are taken

in enormous quantities all over the world, it is tempting to attribute the development of this very serious and baffling condition, agranulocytic angina, which has become so prominent within the past few years, coincident with the increasing use of these drugs. Two points, however, have not received sufficient attention. Few authors have given careful consideration to the actual temporal relation of the drug administration to the hematologic picture, both before, during and after the disease, and too little attention has been paid to the fact that under the name of agranulocytic angina there are undoubtedly several entirely different pathologic entities giving rise to similar hematologic and clinical pictures.

The best criteria for the diagnosis of agranulocytic angina that we know of at present are a greatly reduced white blood cell count with almost complete absence of polymorphonuclear cells and a virtually unimpaired red blood cell and platelet count. There should be no bleeding from the mucous membranes or other surfaces, no enlargement of the lymph nodes not readily accounted for by local sepsis and no notable enlargement of the spleen. At the height of the disease there should be few if any immature white blood cells in the peripheral circulation. Neither the fever nor the ulcerations are characteristic. The latter may be absent. The bone-marrow from the vertebra, sternum and femur should show approximately the same picture, namely a cessation of maturation of the white blood cells at the stem-cell stage. It should be said, however, that the pathologic findings are as yet but little known and probably vary considerably from case to case. There should be no other disease present which could logically explain the leukopenia.

Extreme leukopenia with relative or complete absence of the granular white blood cells is not pathognomonic of a single pathologic entity. Such findings do not by any means make the diagnosis of agranulocytic angina. Yet such is often thought to be the case. Extreme leukopenia is seen characteristically in true agranulocytic angina, not rarely in aleukemic leukemia, sometimes in miliary tuberculosis of the bone marrow, Hodgkin's disease, metastatic bone carcinoma and probably a variety of other obscure conditions. It is found in certain patients with overwhelming sepsis. One etiologic agent cannot underly all these conditions and without question their differential diagnosis during life may be extremely difficult or even impossible. Furthermore, it must be remembered that the prodromal symptoms of agranulocytic angina are frequently such as to call for the administration of antipyretics and it is easy to attribute the subsequent development of signs and symptoms to the therapy given, whereas they may in reality be merely a coincidental series of events. This is particularly the case when the drugs have been given for a brief time only and the leukopenia is discovered shortly afterward.

From our cases presenting what we believe to be the classical

picture of agranulocytic angina, 27 cases have been selected for study. The only basis for this selection has been the possession of accurate and unequivocal evidence as to the administration of amidopyrin and allied drugs. No case which might properly be classed as aleukemic leukemia is included. Those cases which came to autopsy presented findings consistent with the diagnosis of agranulocytic angina. Yet the point must, we believe, be stressed that at present the diagnosis of this condition is fraught with much difficulty, and time alone will tell whether from among the cases showing extreme leukopenia may be segregated a true disease entity. Until such a time it is wise to be guarded in our conclusions as to etiology.

From the table it can be seen that to Patients 1 to 7 the suspected drugs were given in considerable quantities rather regularly and for some time prior to the onset of the recognized disease. In these cases the therapy may tentatively be regarded as causative. The reasons for the administration of such therapy were various, but in no case could it be properly said that the drugs were given for the relief of premonitory symptoms of agranulocytic angina. Thus, approximately 26% of the cases studied may possibly be attributed to the administration of the drug, or at least the therapy may be regarded as having an accelerating factor in a patient already subject to the disease in a subclinical form. There is no absolute proof; but the facts are suggestive. Thus far our data support the thesis of those authors who would incriminate the amidopyrin group of drugs. Of these 7 cases, 5 were adequately treated with Pentnucleotide (N. N. R.) and all are now alive and well. Two received no treatment and died. Madison and Squier³ report that all their patients who continued to take the drug died. Of our 3 patients who continued to take amidopyrin during their attacks, 1 died and 2 recovered. Case 5 continued to take pyramidon regularly and also to have repeated temporary attacks of neutropenia. On withdrawal of all drugs of the amidopyrin series these temporary attacks ceased.

Seven patients (Nos. 8 to 15) were given at various times drugs of the amidopyrin group, and without careful analysis these drugs might easily be incriminated as the cause of the condition. Yet careful scrutiny of the evidence points in the opposite direction. The mortality in this group was 30%. All were treated with Pentnucleotide. It is worth while to examine some of these cases more carefully because, as stated above, without careful scrutiny the amidopyrin might have been incriminated. In Case 9 there was a history of at least 10 major attacks, each occurring at the time of menstruation, with a progressive fall in the average white blood cell level over a year's period. With each attack a lower level was reached. Each recovery was a little less satisfactory. In the midst of her fifth attack she was given 40 grains of pyramidon over a period of 4 days, and during this time her white blood cell count

rose from 800 per c.mm. with no neutrophils to 3700 per c.mm. with 64% neutrophils. During this time she had been under Pent-nucleotide therapy. In another attack she was given 30 grains of pyramidon over a period of 3 days and during this time her white blood cell count rose from 1600 per c.mm. with 1% neutrophils to 3300 per c.mm. with 33% neutrophils and continued rapidly to reach a normal level. Thus, relatively large doses of the drug, even at the height of the disease, had no deleterious effect.

FIG. 1.—THE RELATION OF AMIDOPYRIN AND ALLIED DRUGS TO THE ETIOLOGY OF AGRANULOCYTIC ANGINA.

Case No.	Age.	Sex.	No. of attacks.	Lowest W. B. C. per c.mm.	Lowest neutrophil %.	Drug taken:			Probable relation to disease.*	Result.
						Before.	During.	After.		
1 . . .	88	F	1	500	0	75 days	Yes	0	Causative	Dead
2 . . .	55	F	1	300	0	45 days	Yes	0	Causative	Alive
3 . . .	30	F	1	3200	0	30 days	0	0	Causative	Dead
4 . . .	68	F	1	200	0	30 days	0	0	Causative	Alive
5 . . .	55	F	Many	700	0	3 years	Yes	Yes	Causative	Alive
6 . . .	66	F	1	1000	0	60 days	0	0	Causative	Alive
7 . . .	60	F	1	800	0	14 days	0	0	Causative	Alive
8 . . .	50	F	Many	2900	5	Occ.	0	0	0	Alive
9 . . .	30	F	10	200	0	0	Yes	0	0	Dead
10 . . .	60	M	1	200	0	Occ.	Yes	Yes	0	Alive
11 . . .	50	F	Many	400	0	14 days	Yes	Yes	0	Alive
12 . . .	50	F	1	2600	2	Irregularly	Yes	Yes	0	Alive
13 . . .	38	F	1	300	0	Irregularly	Yes	Yes	0	Alive
14 . . .	25	F	3	1200	0	5 mos. before 1st and 2d, none before 3d	0	0	0	Alive
15 . . .	50	F	3	500	0	5 days	0	0	0	Dead
16 . . .	60	F	9	1000	0	0	0	0	0	Dead
17 . . .	50	F	2	1900	3	0	0	0	0	Alive
18 . . .	60	M	Many	1000	0	0	0	0	0	Alive
19 . . .	50	F	1	600	0	0	0	0	0	Dead
20 . . .	65	F	1	450	0	0	0	0	0	Dead
21 . . .	63	F	1	1100	0	0	0	0	0	Dead
22 . . .	72	F	1	2500	0	0	0	0	0	Alive
23 . . .	35	F	1	1000	0	0	0	0	0	Dead
24 . . .	37	F	1	1000	0	0	0	0	0	Dead
25 . . .	43	F	9	500	0	0	0	0	0	Alive
26 . . .	60	M	2	2000	0	0	0	0	0	Alive
27 . . .	30	F	1	1000	2	0	0	0	0	Alive

Pentnucleotide was given in varying amounts to all but Cases 1, 3, 19 and 21.

Patient 10 took Peralga rather regularly for a week prior to his only attack. He has, however, taken the drug in larger quantities since that time and, although his blood has been carefully studied,

no changes whatsoever have been noted. Clinically he continues to be well and active. In a similar manner both Patients 11 and 12 took pyramidon and allonal before their attacks, but have also taken it more or less regularly since, without the slightest effect on their white blood cells, as evidenced by repeated examinations. Patient 13 had taken pyramidon irregularly for years before her first attack. During her second attack she was given large doses for 5 days and during this time, while under Pentnucleotide therapy, her white blood cell count rose from 300 per c.mm. with no neutrophils to 1500 with 27% neutrophils. Recovery was rapid and complete. Case 15 was given amytal compound for 4 days prior to her first attack for the alleviation of symptoms which might well have been regarded as prodromal. No such drugs were used before her second attack from which she recovered, nor prior to her third and fulminating seizure in which she died. In a similar manner Patient 14 took moderate quantities (30 grains) of pyramidon each month at the time of her menstruation for 5 months prior to her first attack, and somewhat larger doses (40 grains) each month for 4 months prior to her second attack. Since then, however, she has had no drugs of this type whatsoever and yet 9 months later had a third and equally severe seizure from which she recovered spontaneously.

Twelve patients (Nos. 16 to 27) with similar, if not identical, clinical and hematologic pictures, received no drugs of the amidopyrin series whatsoever either before, during or after their attacks. The mortality in this series was 50%. Ten were treated with Pentnucleotide with a mortality of 40%. Clinically the patients in this category differed in no way from those which took the drugs prior to their illness.

Tentative Conclusions. 1. In 26% of the cases studied the disease followed the administration of amidopyrin or allied drugs. That in these instances the disease may have been actually caused by the therapy is possible, perhaps probable.

2. In another 30% of the cases a critical examination of the evidence shows that in spite of the fact that these drugs were taken in considerable quantities they definitely have no causative relation to the disease.

3. Of these patients, 44% received no drugs of this type whatsoever, yet their clinical and hematologic pictures were similar in every respect.

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AUTOHEMAGGLUTINATION.

BY IRVING SHERMAN, M.D.,

HEMATOLOGIST AND TRANSFUSIONIST, ISRAEL ZION, TRINITY AND BROOKLYN
WOMEN'S HOSPITALS, BROOKLYN, N. Y.

(From the Israel Zion and Trinity Hospitals.)

THE phenomenon of autohemagglutination has lately received more attention, particularly in regard to blood transfusions. A complete survey of the literature of the subject has been presented by Boxwell and Bigger,¹ who collected 22 cases from the literature up to 1927, and added 2 cases of their own to the list. In the following years, 5 more cases were reported by Rubaschewa,² Iwai and Mesai,³ Le Goff,⁴ Manheims and Brunner,⁵ and Blenhamou and Nouchy.⁶ To this series of 29, I can add 3 additional cases of autohemagglutination, 2 of which were repeatedly transfused without any untoward reaction.

Case Abstracts. CASE 1.—L. G., aged 55, female, was admitted to the Israel Zion Hospital suffering from lobar pneumonia of both bases. The patient did not have a crisis, and after 3 weeks of fever she became very anemic and a transfusion was suggested. In attempting to type her blood, autohemagglutination was found and transfusion deemed inadvisable.

CASE 2.—F. S., aged 13, female, was admitted to the Trinity Hospital on August 16, 1933, with staphylococcus septicemia and multiple foci of osteomyelitis. The patient remained in the hospital for 6 months and received 5 transfusions. At the time of typing her blood we found that her serum agglutinated her own cells, but upon warming her cells, agglutination occurred only with Type B serum. A Type A donor was used for the transfusions, which were tolerated without any untoward reaction.

CASE 3.—A. G., aged 50, female, was admitted to the Israel Zion Hospital with the diagnosis of influenzal pneumonia and diabetes mellitus. Due to the severe secondary anemia a transfusion was decided upon on the 9th day. While typing her blood it was found that the red blood cells were agglutinated by the patient's own serum, but if the slide was warmed to body temperature the agglutination disappeared and the cells became separated. The patient was then given 500 cc. of Type O blood. She suffered no untoward reaction and 5 days later a second transfusion of 500 cc. of Type O blood was given with equal success.

Discussion. Table 1 demonstrates the behavior of serum and red cells of patient L. G., in relation to sera and cells of all 4 blood groups. This serum agglutinated the cells of all 4 groups as well as her own. The patient's red cells were not agglutinated by any other serum and hence the patient classified in Group O.

If patients' serum was diluted 1 to 16, agglutination occurred at room temperature in all groups, whereas the patient's own cells and other cells of Type O were agglutinated up to a dilution of 1 to 32. At body temperature with the serum diluted 1 to 2, agglutination occurred only with cells of Groups AB, A and B, whereas cells of Type O and the patient's own cells did not clump.

Subsequent studies on the relation of autoagglutination to temperature revealed that this phenomenon occurred only at temperatures below 31.5° C. The clumps of the red cells broke up as soon as the temperature was brought above this critical point.

TABLE 1.—AGGLUTINATION BEHAVIOR OF L.G.'s SERUM AND ERYTHROCYTES.

Serum.	Cells.	Agglutination.
Type AB	L.G.	0
Type A	L.G.	0
Type B	L.G.	0
Type O	L.G.	0
L.G.	L.G.	Clumps

Serum.	Cells.	Agglutination.
L.G.	Type AB	Clumps
L.G.	Type A	Clumps
L.G.	Type B	Clumps
L.G.	Type O	Clumps
L.G.	L.G.	Clumps

Serum L. G.

Cells.	20° C.						37° C.	
	1/2	1/4	1/8	1/16	1/32	1/40	1/2	1/16
Type AB . . .	Clumps	Clumps	Clumps	Few	0	0	Clumps	0
Type A . . .	Clumps	Clumps	Clumps	Few	0	0	Clumps	0
Type B . . .	Clumps	Clumps	Clumps	Few	0	0	Clumps	0
Type O . . .	Clumps	Clumps	Clumps	Clumps	Few clumps	0	0	0
L.G.	Clumps	Clumps	Clumps	Clumps	Few clumps	0	0	0

TABLE 2.—AGGLUTINATION BEHAVIOR OF F.S.'s SERUM AND ERYTHROCYTES.

Serum.	Cells.	Agglutination.
Type AB	F.S.	Clumps
Type A	F.S.	0
Type B	F.S.	Clumps
Type O	F.S.	Clumps
F.S.	F.S.	Clumps

Serum.	Cells.	Agglutination.
F.S.	Type AB	Clumps
F.S.	Type A	Clumps
F.S.	Type B	Clumps
F.S.	Type O	Clumps
F.S.	F.S.	Clumps

Serum F. S.

Cells.	20° C.						37° C.	
	1/2	1/4	1/8	1/16	1/32	1/40	1/2	1/16
Type AB . . .	Clumps	Clumps	Clumps	Clumps	Few	0	Clumps	0
Type A . . .	Clumps	Clumps	Clumps	Clumps	Few	0	0	0
Type B . . .	Clumps	Clumps	Clumps	Clumps	Few	0	Clumps	0
Type O . . .	Clumps	Clumps	Clumps	Clumps	0	0	0	0
F.S.	Clumps	Clumps	Clumps	Clumps	Few	0	0	0

Similar studies with the blood cells and sera of Cases 2 and 3 are presented in Table 2 and Table 3. The findings are identical in all 3 cases, with critical temperature at 30° C. in Case 2 and 30.5 in Case 3. Case 2 belonged to Type A, whereas Case 3 was a Type O like the first case.

TABLE 3.—AGGLUTINATION BEHAVIOR OF A. G.'s SERUM AND ERYTHROCYTES.

Serum.	Cells.	Agglutination.
Type AB	A.G.	0
Type A	A.G.	0
Type B	A.G.	0
Type O	A.G.	0
A.G.	A.G.	Clumps

Serum.	Cells.	Agglutination.
A.G.	Type AB	Clumps
A.G.	Type A	Clumps
A.G.	Type B	Clumps
A.G.	Type O	Clumps
A.G.	A.G.	Clumps

Serum A. G.

Cells.	20° C.						37° C.	
	1/2	1/4	1/8	1/16	1/32	1/40	1/2	1/16
Type AB . . .	Clumps	Clumps	Clumps	Clumps	0	0	Clumps	0
Type A . . .	Clumps	Clumps	Clumps	Clumps	0	0	Clumps	0
Type B . . .	Clumps	Clumps	Clumps	Clumps	0	0	Clumps	0
Type O . . .	Clumps	Clumps	Clumps	Clumps	Few	0	0	0
A.G.	Clumps	Clumps	Clumps	Clumps	Few	0	0	0

While we did not dare to transfuse Case 1, we decided to resort to transfusion as a life-saving procedure on Cases 2 and 3, in spite of the abnormal behavior of their blood. All precautions were taken to forestall the occurrence of autoagglutination in the patients, incidental to a lowering of their body temperature. Twenty minutes prior to the performance of the transfusion, an electric baker was applied to their chests and extremities. The arm was wrapped in an electric hot pad and kept there during the entire procedure. Case 2 received 300 cc. of blood at her first transfusion and tolerated this without any untoward reaction. Case 3 received 500 cc. of blood and subsequently other transfusions of also 500 cc., which were equally well tolerated.

These experiences seem to prove that transfusions are not more dangerous to patients showing autohemagglutination than to other persons. The additional warming of the patient's body is perhaps not absolutely necessary, but adds an additional margin of safety.

The blood of Case 3, examined several weeks later, at a time when her temperature had returned to normal, did not show autoagglutination at room temperature any more. The phenomenon,

however, could be elicited by placing the serum and red cells in the ice box for 5 minutes. At room temperature the cell clumps broke up again and agglutination disappeared. In all 3 cases, similarly to most previous observations, autoagglutination occurred in the course of a febrile infectious condition.

Two patients suffered with pneumonia and the third with osteomyelitis due to staphylococcus infection. Only 1 of the 3 patients (Case 3) had a slight degree of jaundice. Anemia of a severe secondary type was present in all 3 cases. The spleen was enlarged in Case 1.

The relative rarity of autoagglutination and its coincidence with severe infection, anemia and affections of liver or spleen is again emphasized by these 3 observations. It was claimed recently by Rubaschewa² that autoagglutination occurred also in perfectly healthy people but was usually not detected in the course of ordinary blood counts, which are done with diluted blood and, therefore, reveal only instances of autoagglutination if the titer of the serum is at least 1 to 200. While this objection is pertinent, autoagglutination still appears to be rare, if this phenomenon was observed only 3 times in the course of typing and matching with undiluted blood in a series of approximately 2000 transfusions which I have performed during the past 7 years.

Summary. Three cases are reported in which autoagglutination of the red blood cells occurred at room temperature and disappeared at body temperature.

The phenomenon is due to the presence of agglutinins in the serum which produce clumping of red blood cells of all 4 blood groups at temperature below a critical point. This point is between 30° and 31.5° C.

Two of the cases reported belong to Group O and 1 to Group A.

All 3 cases were suffering with a febrile infectious condition. Reëxamination in 1 case, after recovery of the patient, showed diminution of the agglutinating power of the serum to an extent that the clumping of the red cells occurred only in the ice box, but not any longer at room temperature.

Two of the 3 patients received blood transfusions 5 and 2 times respectively, without any untoward reaction.

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ESTIMATION OF CARDIAC TRANSVERSE DIAMETER IN CHILDREN AND COMPARISON WITH CARDIAC AREA.

By WAYNE GORDON, M.D.,

INSTRUCTOR IN MEDICINE UNDER THE LASKER FOUNDATION, UNIVERSITY OF CHICAGO,
AND

WRIGHT ADAMS, M.D.,

INSTRUCTOR IN MEDICINE, UNIVERSITY OF CHICAGO,
CHICAGO, ILL.

(From the Department of Medicine of the University of Chicago.)

THE desirability of expressing cardiac enlargement in mathematical terms has led to the use of various methods of measuring cardiac shadows by means of the Roentgen ray, either in orthodiagrams or in films. Of the various measures two of the most useful have been cardiac area and transverse diameter, each compared with some standard of normal for those measures. The normal standards have been derived from height, age, weight, transverse diameter of the thorax, and various other measures. P. C. Hodges and Eyster¹ derived regression equations for calculating normal cardiac areas in adults from height, weight, and age, and F. J. Hodges and Eyster² derived similar equations for the prediction of normal transverse diameter. Literature with regard to methods is cited in these papers.

P. C. Hodges and the writers have studied a group of normal children and in another paper³ have presented the equation for prediction of cardiac area which appeared most useful in the examination of children. We are indebted to Dr. Hodges for the privilege of further study of this material. The study on children was undertaken because the formula of P. C. Hodges and Eyster derived from adults was found to be unsatisfactory in predicting the normal frontal plane area in children. It will be shown that the relative usefulness of area and transverse diameter in making normal predictions as well as the formulas themselves is different in children. It is the purpose of the present paper to present equations for the prediction of transverse diameter and to evaluate as far as possible the merits of the two measures of heart size as applied to children.

Sources of Data. The subjects of the study were normal children living at the Mooseheart City of Childhood,* Mooseheart, Illinois, aged 2.9 to 18.8 years and of divers builds. Teleroentgenograms were made with a target-film distance of 72 inches and with exposure times ranging from a half second upward. Orthodiagrams were made also, but because of the fact that they were impracticable in the youngest children the measurements of the films were used in the calculations. Careful physical examinations were done on the day of the Roentgen ray examination, and the height,

* The study was made possible through the coöperation of the administration of Mooseheart and of the Mooseheart Laboratory for Child Research, under the direction of Dr. M. L. Reymert.

weight, and sitting height were measured at the same time. Ages were obtained from the records of the institution and verified by the statements of the children. After rejection of all subjects with definite or suspicious evidence of cardiac disease, and of films that were technically unsatisfactory, the series comprised 85 boys and 84 girls.

Areas and diameters were measured on film tracings and the results corrected for distortion due to divergence. To obtain the correction factors the anteroposterior chest diameter was measured on 5 children of a wide range of size and build and the distance from the chest wall to the film as it lay in the cassette holder was measured. The anteroposterior diameters ranged from 9 to 15 cm.; the distance from chest to film was uniformly 1.7 cm. The assumption was made on the basis of lateral chest films from these children that the central plane of the heart and presumably the major part giving rise to the borders of its shadow lay at about one-third the distance from the anterior to the posterior chest wall. This observation corresponds to that of Bardeen⁴ on adults. The object-film distance was estimated on this assumption, and, the target-film distance being uniformly 182.5 cm., the target-object distance was obtained. The correction factor could thus be calculated by the formula,

$$\text{Factor} = \frac{182.5 - (\frac{1}{3} \text{ A. P. Diam.} + 1.7)}{182.5}$$

This fraction is squared for application to area. The correction factors estimated for area lay between .92 and .95; for diameter between .96 and .98. In applying the factors to areas .930 was used for children over 10 years of age, and .945 for children under 10; in applying them to diameters .97 was used throughout.

Work now in progress on adults, with an apparatus in which the film is at a greater distance from the chest wall, and with subjects in whom the anteroposterior chest diameters are greater, indicates a possible advantage to the calculation of a correction factor from the anteroposterior chest diameter of each individual. Anteroposterior diameters were not measured in this series, but in view of the small range of the correction factors in 5 subjects it is likely that no substantial error has been introduced.

It should be noted, also, that a correction for distortion due to divergence does not imply any assumptions with regard to other sources of difference between orthodiagrams, slow films, and rapid films. These observations refer only to the slow film, although we feel it likely that they will also prove applicable to the orthodiagram.

An explanation of the symbols used in tables and equations is given in Table 1.

TABLE 1.—NOTATION.

- A—Age in years.
- H—Height in cm.
- Si—Sitting height in cm.
- W—Weight in kg.
- F—Frontal plane area from film in sq. cm., corrected for divergence.
- \bar{F} —Predicted frontal plane area in sq. cm.
- D—Transverse diameter in cm., corrected for divergence.
- \bar{D} —Predicted transverse diameter in cm.
- M—Mean.
- σ —Standard deviation in the units of measurement of the variable to which it applies.
- R—Correlation coefficient.
- S—Standard error of estimate in the units of measurement of the variable to which it applies.

Statistical Analysis. Accurate definitions of statistical terms and details of the principles of statistical analysis are not within the scope of this paper, but some explanation may be of assistance to those unfamiliar with statistical methods.

The *mean* is the arithmetical average. The *standard deviation* is a measure of dispersion of measures about their mean. It is the square root of the average of squares of deviations of the measures from the mean. *Correlation coefficients*, as used in this paper, are numbers between zero and one, when positive correlation is present, representing the degree of relationship of one series of measures with one (*zero order correlation coefficient*) or more (*multiple correlation coefficient*) other series of measures on the same group of individuals. When one series of measures tends to decrease as the others increase the correlation is said to be negative and the coefficient is between zero and minus one. A correlation coefficient of zero denotes a complete lack of relationship and signifies that one measure is of no value in predicting the other. A correlation coefficient of one or minus one denotes complete mutual interdependence. A *regression equation* is an equation used to apply correlation coefficients to the prediction of one set of measures, the *dependent variable*, from one or more other sets of measures, the *independent variable* or variables, due allowance being made for intercorrelation between the independent variables when more than one is used. The *standard error of estimate*, while calculated in actual practice from correlation coefficients and standard deviations, represents the square root of the average of the squares of all differences between observed and predicted values of the dependent variable.

Graphs of the combinations in pairs of the variables, cardiac area, transverse diameter, height, sitting height, age and weight revealed relationships sufficiently near to straight lines to justify the application of the Pearson product-moment formula and the development of regression equations. The determinant method was utilized for the multiple correlations; the methods are described in standard statistical textbooks such as that of Kelley.⁵

TABLE 2.—MEANS, STANDARD DEVIATIONS, AND ZERO ORDER CORRELATION COEFFICIENTS.

	M	σ	Zero order correlation coefficients.					
			D	F	H	Si	A	W
D	9.89	1.178	1.000					
F	77.36	21.02	1.000				
H	139.2	22.28	.769	.887	1.000			
Si	74.81	10.07899	.966	1.000		
A	11.06	4.04	.724	.860	.917	.919	1.000	
W	36.94	14.98	.810	.923	.935	.950	.908	1.000

Zero order correlation coefficients, means, and standard deviations are listed in Table 2. Cardiac area correlates better with the other measures than does transverse diameter. Both measures correlate better with weight than with height, and with height than with age. The correlations of the independent variables one with another indicate that either height or sitting height may be used, but that there is little likelihood of value in using both in the same formula. Age correlates quite well with both height and weight. Similar quantities were calculated for the sexes separately, but because the advantage in accuracy was slight when multiple correlations and regression equations were developed, these figures are dropped from further consideration.

Eleven equations were developed for prediction of cardiac area and four for prediction of transverse diameter. Sitting height offered a slight advantage over height in some formulas, insufficient in our opinion to justify the greater inconvenience of measurement, as the difference in the multiple correlation coefficient varied from .000 to .003. The formulas derived from some combinations of variables are listed in Table 3. With each formula is given the multiple correlation coefficient and the standard error of estimate; standard errors of the coefficients are indicated directly beneath the coefficients. Accuracy of prediction is indicated by the standard errors of estimate and by the correlation coefficients; the probability of general usefulness of measures is indicated by the standard errors of their coefficients.

TABLE 3.—EQUATIONS FOR THE PREDICTION OF CARDIAC AREA AND TRANSVERSE DIAMETER.

(The standard error of each of the coefficients is indicated beneath the coefficient.)

Equation.					R	S
$\bar{F} = .405$.213	Si +	.300 .397	A +	.970 .135	W + 7.9	.929 7.77
$\bar{F} = .180$.078	H +	1.045 .116	W +	13.7	.925	7.97
$\bar{D} = .00851$.0075	H -	.0369 .0352	A +	.0615 .0107	W + 6.8	.817 .680
$\bar{D} = .00490$.00677	H +	.0569 .0101	W +	7.1	.811	.689
$\bar{D} = .0637$	W +	7.5			.810	.690

The probable error of estimate, sometimes used in statistical work, is a measure which may be used instead of the standard error; it is .67449 times the standard error, and designates the range within which the best half of the predictions may be expected to fall in a normal distribution of errors. In a group of measures with such a distribution of errors, half of the observed measures will vary from the predicted measure by an amount exceeding the probable error of estimate. Since positive and negative errors are presumably equally frequent, half of these, or one-fourth of the entire group, will exceed the predicted measure by more than the probable error of estimate. This fact does not justify the conclusion drawn in some other papers on the Roentgen ray measurement of heart size that three-fourths of the hearts that exceed the predicted heart size by more than the probable error of estimate are pathologically enlarged. While the conclusion may be drawn properly that the probability of this class among normal hearts is one-fourth, the conclusion that the probability of normality of hearts in this

class is also one-fourth is in serious error when the data are derived entirely from normal subjects.

In the prediction of cardiac area there is a slight advantage in correlation coefficient and standard error of estimate in using age as one of the variables; the standard error of the coefficient of age, however, is in excess of the coefficient itself. In a series of this size it is considered unlikely that a measure will be of value when applied to other populations if the standard error of its coefficient is in excess of half the coefficient. For this reason it is possible to drop age as a variable and thus make the formula more conveniently applicable without any sacrifice of accuracy. In the formulas for the prediction of transverse diameter the use of height increases the correlation by .001 and the use of height and age increases the correlation by .007 above the correlation with weight alone. The standard errors of the coefficients of age and height are large, however, in comparison with the coefficients, hence these formulas may not be expected to predict transverse diameters generally appreciably better than the formula involving weight alone. The formulas chosen as statistically satisfactory, therefore, are:

$$\begin{aligned} F &= .180 H + 1.045 W + 13.7 \\ \bar{D} &= .0637 W + 7.5 \end{aligned}$$

Comparison of Results. In comparing the accuracy with which each of these cardiac measures may be predicted, the standard errors form a satisfactory means of comparison. It is obvious, however, that an error of, say 5%, is of greater significance in a group of measures ranging from 90% to 110% of a mean than in a group ranging from 70% to 130% of its mean. In other words, the significance of an error is distinctly dependent on the degree of dispersion of the series of measures. Since the measure of dispersion used in the calculation is the standard deviation, a true comparison of the standard errors of estimate requires that they be expressed in terms of standard deviations of the quantities to which they apply. The quantities, standard error of estimate divided by standard deviation, are the coefficients of alienation, usually designated by the letter *K* (Fig. 1). Included with this graph is a comparison of the coefficients of alienation derived from the figures of P. C. Hodges and Eyster and of F. J. Hodges and Eyster* for adults.

To determine the relative accuracy of prediction for different portions of our series we have determined the difference between predicted and observed cardiac area, and the difference between predicted and observed transverse diameter in each subject. The absolute value of the individual errors has been averaged by height

* The probable error of estimate given by F. J. Hodges and Eyster is smaller than would be indicated from their data; it appears that they failed to extract the square root of the term $1-R^2$ in the formula for its calculation. Apparently this error did not affect the rest of their figures. We have calculated the standard error of estimate from their multiple correlation coefficient,

classes, and the results are expressed in a graph (Fig. 2). In this graph, for proper comparison, the errors in each measure are expressed as fractions of the standard deviation of that measure. The greater accuracy of prediction of cardiac area appears constant throughout the group.

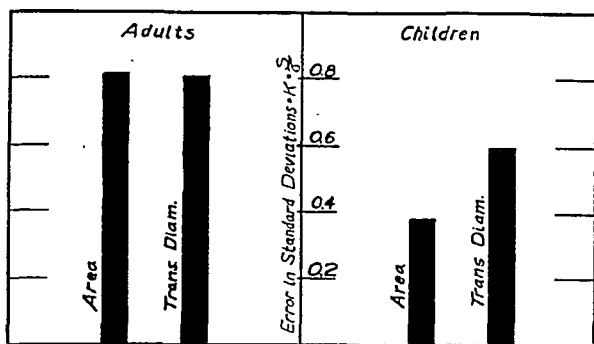


FIG. 1.—Standard errors of estimate in terms of standard deviations (coefficients of alienation).

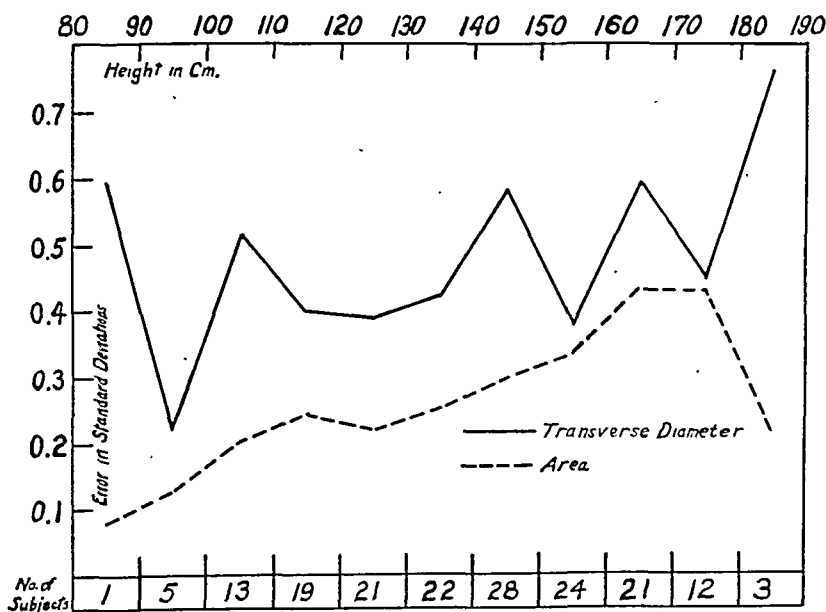


FIG. 2.—Average error in predictions of cardiac area and transverse diameter by height classes, expressed as fractions of their respective standard deviations.

The papers referred to previously indicate that the cardiac area and the transverse diameter may be predicted in adults with practically equal accuracy. The correlation coefficients are .579 and .588, and the standard errors of estimate are .814 and .810 standard deviations respectively. In children, on the other hand,

the correlation coefficients are .925 and .810, and the standard errors .379 and .587 standard deviations respectively. The complete explanation for the difference between adults and children in this respect is not evident. The difficulty in locating the lower border of the heart, one of the greatest sources of error in estimating cardiac area, is considerably less in our experience in children than in adults; this may be responsible in part for relatively better measurement of area. It is also worthy of note that the negative correlation between height and transverse diameter present in adults is not present in our series of children. When age and height are both used with weight there is some negative correlation with age, subject, however, to sufficient error that it may be peculiar to this series. It is possible that the relationship between height and age, on the one hand, and transverse diameter, on the other, undergoes considerable change from one end of our series to the other, if the influence of weight be held constant.

With regard to the apparently greater accuracy of predictions of each of the cardiac measures in children than in adults mathematical deductions may be misleading. While the "efficiency" of the prediction formula $(1-K)$ is considerably greater in each case in children than in adults, it must be remembered that the efficiency of the formula denotes the amount of improvement of the prediction over a random guess for each individual at the mean. In a group such as children in whom all the bodily measurements vary through a wider range in proportion to their mean values, the prediction may be expected to move relatively farther from the means than in adults. For this reason the statistical measures of efficiency used here are not mathematically comparable in groups covering widely different ranges of measures, although they are a reliable guide in comparing different sets of measures in similar or identical groups. It will be noted that our comparisons on smaller groups than the entire series are based on actual observed differences between observed and predicted measures.

The ultimate answer to the question of which is the better method of estimating heart size does not depend entirely on the accuracy with which each of the quantities can be predicted. Since measures of heart size are used in practice for the separation of normal from enlarged hearts, the value of a method depends in practice on how well it separates hearts that appear to be normal from those in which there is other reason to believe that the heart is enlarged. This test has not been applied, so far, to our formulas. Eyster⁶ has applied it to several methods of measuring the heart in adults and found that, in spite of approximately equal accuracy of prediction in the normal, the cardiac area method separated the normal from the abnormal somewhat better than any method involving transverse diameter which he used. While such a test of these formulas is desirable, it would appear unlikely that transverse diameters

predicted with so much less accuracy in the normal, as appears from these figures, could separate normals from abnormals with greater accuracy than cardiac area determinations.

Summary. 1. The relations of cardiac area and cardiac transverse diameter, as measured by the Roentgen ray, to sitting height, height, weight, and age have been studied in a group of normal children.

2. Both measures correlate better in children with weight than with height or age.

3. An equation is presented for the prediction of normal transverse diameter and a comparison is made with cardiac area prediction formulas previously published from the same material.

4. Cardiac area in normal children can be predicted with greater accuracy than transverse diameter by any of the measures used. The advantage of cardiac area over transverse diameter as a measure of normal heart size appears to be greater in children than in adults.

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THE Q WAVE IN THE ELECTROCARDIOGRAM.

BY ALBERT W. WALLACE, M.D.,

WATKINS GLEN, N. Y.

(From the Department of Cardiology, The Glen Springs.)

SINCE 1930, when Pardee,¹ made a critical study of 43 cases showing a significant Q wave in the third lead of the electrocardiogram, other papers have appeared further analyzing records showing this wave.²⁻⁸

The Q_3 wave rarely appears in normal individuals. In a series of 277 normal cases, Pardee,¹ found a Q_3 wave in only 2 records, and Edeiken and Wolferth,³ found a Q_3 wave in only 1 record out of 826 electrocardiograms, and in this 1 case it was later found that the individual had a cardiac lesion. From the electrocardiograms of the 1103 normal individuals thus examined for a Q_3 wave, it was found, therefore, in only 2 cases or an incidence of only 0.18%.

Factors other than heart disease, however, have been shown to cause in some cases a Q_3 wave. Krumbhaar and Jenks,⁹ observed a Q_3 as a common finding in the electrocardiograms of infants 2 to 12 months of age. Any condition which will elevate the diaphragm

and rotate the heart to the left may result at times in a Q_3 wave.^{1,3,5} The short, thick-set, hypersthenic type of chest with a high diaphragm, or ascites or gas distending the abdomen,⁵ and thus elevating the diaphragm, may at times cause a Q_3 wave. Pregnancy,^{1,3,10} especially in the later months, in some cases probably acts in a similar manner, for all cases which showed a Q_3 during pregnancy did not show it when electrocardiographed after delivery. Respiration,^{1,5} likewise has been shown to effect the size of the Q_3 wave, becoming larger with expiration and the resulting elevation of the diaphragm, and smaller with inspiration. France⁶ stresses the fact that coronary disease often occurs in the elderly, obese, thick-set individual, so that lateral displacement of the heart must be considered, in this type, before placing too much significance in a Q_3 wave which might be present.

In going through our files we found 125 electrocardiograms showing a Q_3 wave which conformed to the criteria for a significant Q_3 wave as laid down by Pardee.¹ Cases included in this study are those in which:

1. The Q_3 wave was at least 25% of the greatest R in any lead; (2), the initial downward deflection (Q) was followed by an upright deflection (R) without an S wave; (3) records showing a Q_3 wave but where the R_3 was greater than the R_2 and all so-called M or W complexes were omitted.

Of the 125 cases found some were referred for an electrocardiogram only, so that complete histories were not available in these cases. The histories of 108 cases, however, were complete and satisfactory for a critical study, and an analysis of these cases is given in Table 1.

TABLE 1.—AN ANALYSIS OF 108 CASES OF SIGNIFICANT Q_3 WAVE RECORDS.

	No.	%
Total cases	108	
Angina pectoris	54	50
Hypertension	14	13
Arteriosclerotic heart disease not above	22	20
Preceding coronary thrombosis	4	3.7
Other forms of heart disease:		
Rheumatic heart disease	2	1.8
Thyrotoxicosis	1	0.9
Unclassified group	11	10

Nine cases of angina pectoris had hypertension making a total of 23 cases having hypertension.

Twenty cases gave a history of a previous coronary thrombosis, 16 of these also having either angina pectoris or hypertension and so being classified in the latter groups.

Fifty-four (50%) had angina pectoris. In this group are included all cases of typical clinical angina pectoris, characterized by attacks of substernal pain brought on by exertion and relieved by nitrites. Of these cases 9 also had hypertension but were included in the group.

Fourteen (13%) had hypertension which includes all cases not having the anginal syndrome, but whose blood pressure was elevated above 150 systolic and 100 diastolic.

Twenty-two (20%) are classified under arteriosclerotic heart disease, not having angina pectoris or hypertension. These cases showed cardiac disease characterized by arteriosclerosis, and dyspnea on exertion, or signs of congestive heart failure. Many of these cases undoubtedly represent coronary disease which could not be classified under the angina pectoris or hypertension group.

Four (3.7%) gave a history of a typical preceding attack of coronary thrombosis, diagnosed as such, but which was not preceded or followed by any signs of heart disease except for the presence of a moderate degree of arteriosclerosis. In all, 20 of our cases (18%) gave a preceding history of a coronary thrombosis which occurred anywhere up to a year previous to the time our record was taken. Of these 16 had either angina pectoris or hypertension and so are classified under the latter groups.

There were 2 cases of rheumatic heart disease and 1 of thyrotoxicosis with cardiac involvement.

Eleven cases (10%) were placed in an unclassified group. Of these 3 showed vague heart symptoms which could not be definitely classified, while the remaining 8 cases had no heart symptoms. Of these 8 cases there was 1 of pernicious anemia, 1 of empyema of the gall bladder, and 2 of intestinal stasis. Of the 11 cases there were 6 of obesity in the short, heavy-set type, and it may be that the Q_3 wave was caused by an elevated diaphragm in some of these cases. Two others suffered from a severe degree of flatulence, which has also been shown to cause a Q_3 wave at times.

In order to determine if possible the significance of a record showing a Q_3 wave alone, from records which exhibited other abnormalities besides the Q_3 wave, our cases were divided into two groups, termed normal and abnormal respectively and are seen in Table 2.

TABLE 2.—AN ANALYSIS OF NORMAL AND ABNORMAL $Q R S T$ WITH A Q_3 .

	Normal cases.	Group %	Abnormal cases.	Group %
Angina pectoris	18	38	36	60
Hypertension	2	5	12	20
Previous coronary thrombosis	0	0	4	6
Arteriosclerotic heart disease not above	15	32	7	11
Rheumatic heart disease	2	5	0	
Thyrotoxicosis	1	2	0	
Unclassified group	9	19	2	3
Total	47		61	
Total cases having hypertension	4		19	
Total cases having had a previous coronary thrombosis	0		20	

The normal group includes those records which showed a normal record except for the presence of a Q_3 wave, and includes those

records with a negative T in the third lead. Under the abnormal classification are included those cases which in addition to the Q_3 wave showed slurring of the $Q R S$ in more than one lead, or T wave negativity in Leads I, I and II, I, II and III, or II and III. There were 47 cases classified under the normal group and 61 cases under the abnormal group.

Angina pectoris was present in 60% of the abnormal group, while present in 38% of the normal group. France,⁶ in a similar analysis of 32 cases in each group found a higher percentage of angina pectoris in the abnormal group (72%) and a much smaller percentage (9%) in the normal group.

The incidence of hypertension is also higher in the abnormal group, while those cases which could not be classified as having any coronary disease are more frequently seen in the normal group.

From these findings it would appear that the incidence of coronary disease is higher in patients whose electrocardiograms show other abnormalities besides a Q_3 wave, and that in the absence of other abnormalities a record which shows a Q_3 alone is more often found in those who have no coronary disease.

Pardee¹ stresses the significance of the relative size of the Q_3 wave as compared to the greatest R in any lead, stating that when the Q_3 was 50% or more of the maximal excursion, 73% of his cases had angina pectoris. Pardee says that the large Q_3 is associated with any pathologic changes that involve coronary narrowing and it would seem that the larger the Q in relation to the $Q R S$, the closer the relationship.

Ziskin⁵ states that in his series when a Q appeared which was 50% or more of the greatest R , 65% had coronary disease.

Because of the great variation in the size of the R waves in different records, and in order to see whether it was the ratio of the Q_3 to the greatest R , or the actual size of the Q_3 itself, irrespective of the size of the R , Tables 3 and 4 were prepared.

TABLE 3.—SIGNIFICANCE OF THE RATIO OF THE Q_3 TO THE GREATEST R .

	Ratio of the Q_3 to the greatest R expressed in percentage.						
	No. % 25-35	No. % 36-45	No. % 46-55	No. % 56-65	No. % 66-75	No. % 76-85	No. % 86-100 over 100
Total cases	22	26	17	13	14	4	4
Angina pectoris	10-45	10-38	6-35	7-54	8-57	3-75	6-75
Hypertension	1-5	5-19	2-12	1-8	3-21	1-25	1-12
Arteriosclerotic heart dis- ease not above	5-23	4-15	9-53	2-15	1-7	0	1-12
Rheumatic heart disease	2-9	0	0	0	0	0	0
Thyrototoxicosis	0	1-4	0	0	0	0	0
Unclassified group	3-14	5-19	0	2-15	1-7	0	0
Preceding coronary thrombosis	1-5	1-4	0	1-8	1-7	0	0
Total hypertension	2	7	3	2	4	2	3
Total coronary thrombosis	1	5	1	6	3	1	3

It will be seen from these two tables that the actual size of the Q_3 wave alone is of more significance than is its ratio to the greatest

R , and that the deeper the Q , the greater the significance. While the percentage of the ratio of the Q to the greatest R increases as the incidence of coronary disease increases, it does not do so in as proportionate a manner as it does in Table 4, where the size alone of the Q wave is taken.

TABLE 4.—SIGNIFICANCE OF THE DEPTH OF THE Q_3 WAVE.

	Size or depth of Q_3 in millimeters.			
	To 3 mm. No. %	3 to 5 mm. No. %	5 to 7 mm. No. %	Over 7 mm. No. %
Total cases	28	44	20	16
Angina pectoris	10-36	19-43	13-65	12-75
Hypertension	1-4	4-9	5-25	4-25
Arteriosclerotic heart disease not above	12-43	10-23	0	0
Thyrototoxicosis	0	1-2	0	0
Unclassified group	3-11	7-16	1-5	0
Preceding coronary thrombosis	1-4	2-5	1-5	0
Total hypertension	1	9	5	8
Total coronary thrombosis	5	8	2	5

From Table 4 it would seem that a record which shows a Q_3 of 5 mm. or over in depth probably represents a record from a serious case of heart disease. Only 1 case exhibiting no cardiac symptoms was seen in records with a Q_3 of 5 or more mm. in depth. Cases of previous coronary thrombosis were about equally divided among different Q_3 sizes and ratios, and were unexpectedly seen with greater frequency in the records with smaller Q_3 waves.

In many electrocardiograms exhibiting a Q_3 wave, a Q_2 wave was noted also, and because of the relative frequency with which this wave was seen, a study of these cases was made. Cases which exhibited a Q_3 wave, which followed Pardee's criteria and also a Q_2 wave, were selected. The Q_2 was chosen if it was a well-defined wave and was not followed by an S_2 wave greater than the Q_2 . No restrictions were made on the depth of the Q_2 or its relationship in size to the R as was done in the selection of Q_3 records. In 8 cases an S_2 wave was seen which was larger than the Q_2 and these records were eliminated from this study. In 1 case a small S_2 was seen which was smaller than the Q_2 and was included in our group of Q_2 and Q_3 cases.

Of the 108 cases 34 showed a significant Q_2 as well as a Q_3 , this representing a total of 31% of the Q_3 group (Table 5).

TABLE 5.—AN ANALYSIS OF 34 CASES SHOWING A Q_2 AND Q_3 WAVE.

	No.	%
Angina pectoris	23	67
Hypertension	6	18
Arteriosclerotic heart disease not above	5	15
Total cases	34	100

A total of 9 cases had hypertension (3 of these also had angina pectoris).
A total of 8 cases had a preceding coronary thrombosis.

It will be seen that 23 cases (67%) were classified as having angina pectoris, while hypertension and the arteriosclerotic group made up the other 33% of records. Eight cases (23%) gave a history of a previous coronary thrombosis.

Fenichel and Kugell² record 6 cases in which a large Q_2 was seen and in 2 of these the Q_2 was even larger than the Q_3 , while in another the Q_1 was the largest. Myocardial infarction with septal involvement was found in all 7 cases. They state that while this data is insufficient to draw any conclusions, it would seem that a large Q_2 or Q_1 , normally infrequent might have the same significance as a large Q_3 .

It would appear from our 34 cases and Fenichel and Kugell's 7 cases, which came to autopsy, that the presence of a Q_2 and Q_3 is of more significance than is the presence of a Q_3 alone. In our group the high percentage of angina pectoris and the absence of other forms of non-coronary disease is, we feel, significant.

Pardee¹¹ in 1920 described a case of coronary thrombosis in which a Q_3 wave appeared and since then it has been described by others.^{12,13,14}

Levine's series¹² of 82 cases of coronary thrombosis show a Q_3 wave in 40% of cases. Parkinson and Bedford,¹³ noted a Q_3 wave in 9 cases of coronary thrombosis. Edeiken and Wolferth,³ illustrate a record of Q_3 developing after occlusion which was not present before.

Figure 1 represents a case of coronary thrombosis which has been followed by frequent electrocardiograms. Following the attack, the electrocardiogram was typical of coronary thrombosis, showing a high take-off of the $S-T$ segment, in Leads II and III, and a Q_2 and Q_3 wave. As healing took place, the $S-T$ segment took off nearer the isoelectric line, and the T wave negativity first increased, and then decreased. The Q_3 , which in the first record after the attack was quite large, decreased in size and then later increased. On July 17, 1929 the record shows besides the Q_2 and Q_3 (which are as prominent as before), T wave negativity in Leads II and III, but nothing characteristic nor diagnostic of the coronary thrombosis which had occurred only 2 months before.

Figure 2 represents the same case as in Fig. 1, almost a year after the acute attack. The T wave in Lead II has now become diphasic, and in Lead III almost isoelectric. The Q_2 and Q_3 remain, however, and are even greater in depth than in the records taken previously.

We believe that a large Q_3 , and especially a record showing a Q_2 and Q_3 wave, is very significant, and believe with Fenichel and Kugell,² that the Q wave is often the only remaining graphic evidence in the electrocardiogram of the remains of a pathologic process which at one time was acute. We believe that many cases showing a Q_3 and many more showing a Q_2 and Q_3 are cases which at

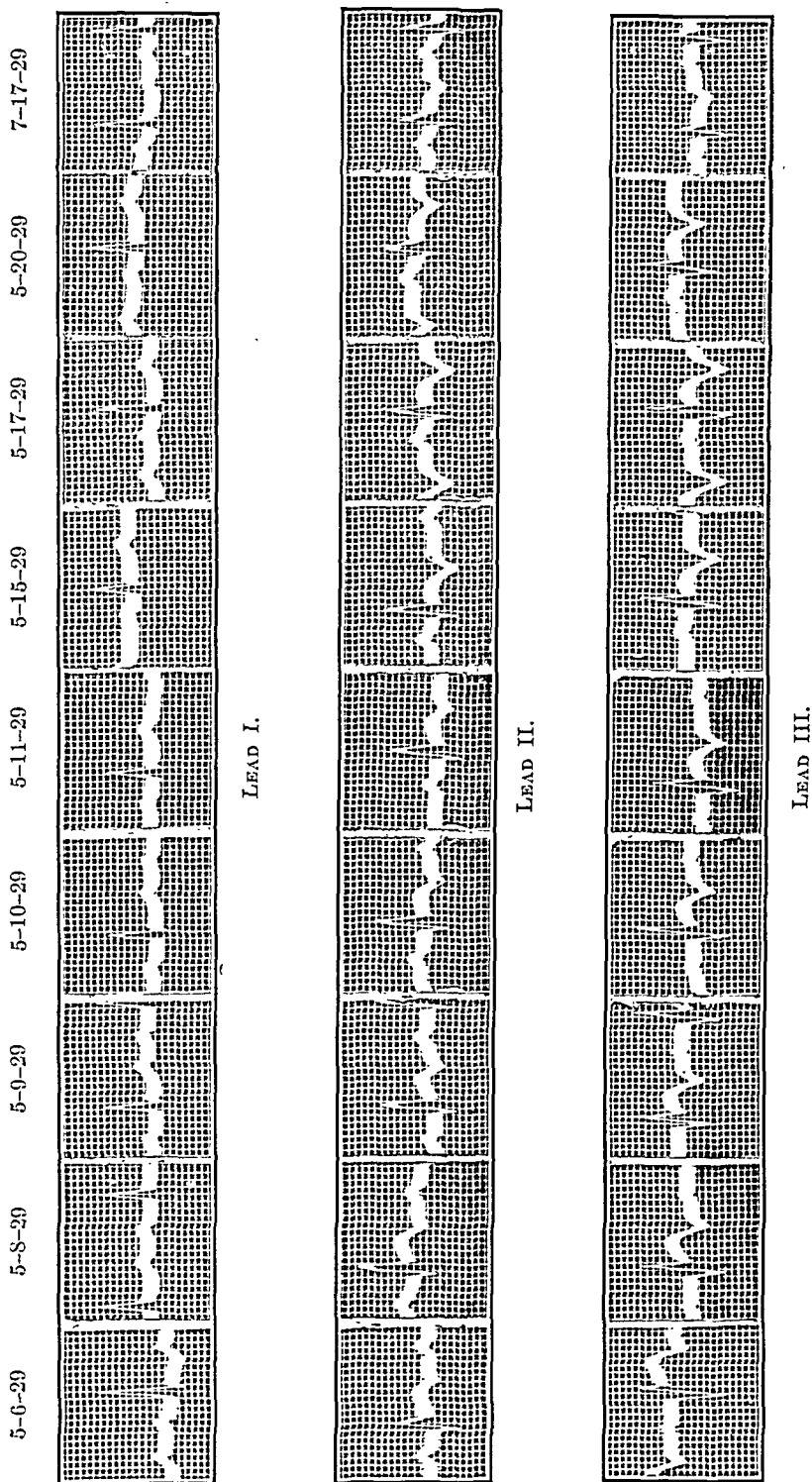


Fig. 1.—Coronary thrombosis. The acute attack occurred 48 hours before the first record taken on May 6, 1929. Note the persistence of the deep Q_2 and Q_3 waves throughout the series.

some previous time suffered from an acute severe myocardial ischemia, and went possibly diagnosed either as a severe attack of angina or went unsuspected.

While the presence of a Q_2 and Q_3 wave is more uncommon than a Q_3 wave alone, we believe that when it is seen, its significance is much greater than when a Q_3 wave alone is noted.

Two of our cases of Q_2 and Q_3 , which were normal records in every other respect, gave definite histories of a preceding coronary thrombosis.

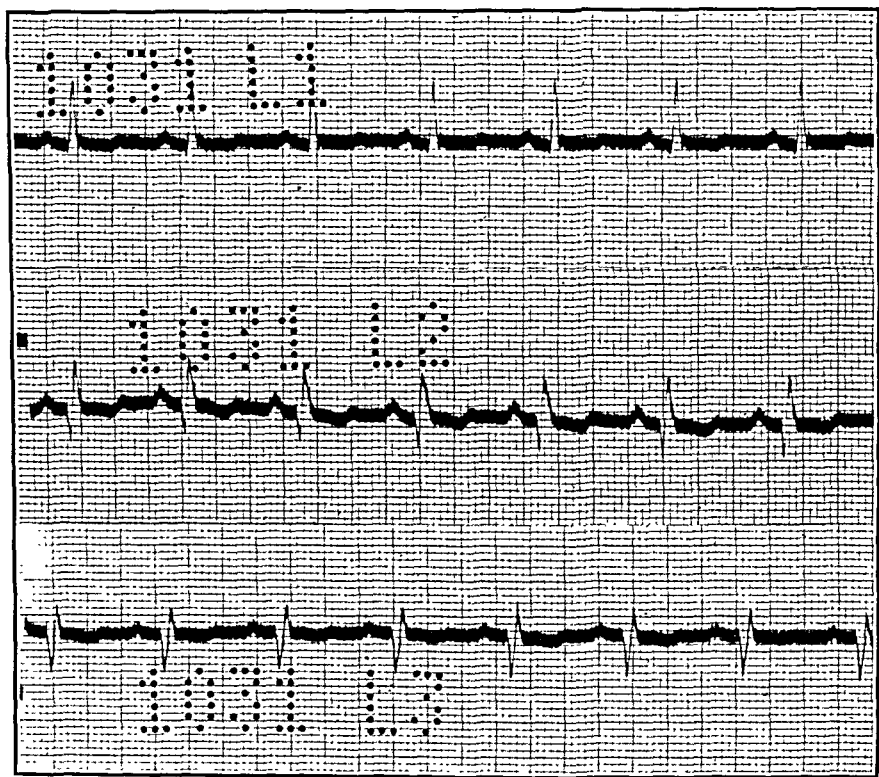


FIG. 2.—From the same case as Fig. 1, taken April 23, 1930 almost 1 year after the acute attack of coronary thrombosis. Note that the Q_2 and Q_3 waves still persist, and are even larger than in the records taken soon after the acute attack, while other signs of coronary thrombosis have disappeared from the record.

Summary and Conclusions. Of 108 cases showing a significant Q_3 wave, angina pectoris was found in 50% and hypertension and arteriosclerotic disease of the heart in 33%.

An electrocardiogram which shows in addition to the Q_3 wave, other abnormal changes, is seen more frequently in coronary disease, although coronary disease is seen frequently enough in the electrocardiograms showing nothing abnormal (except for the Q_3 wave) to be significant.

The depth of the Q wave alone is of more significance than is its ratio to the greatest R , and Q waves of more than 5 mm. in depth were found to be very significant.

A Q_2 and Q_3 wave, when present in the same record, is of more significance than is the presence of a Q_3 wave alone, and we believe that many cases showing a Q_2 and Q_3 wave represent cases of a previous coronary thrombosis in which the Q waves are the only remaining graphic sign of heart damage.

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AORTIC STENOSIS OF INFLAMMATORY ORIGIN WITH A DIFFERENTIAL STUDY OF THE ACQUIRED OR CONGENITAL ORIGIN OF A BICUSPID AORTIC VALVE.*

BY LOUIS FAUGERES BISHOP, M.D., Sc.D.,

CONSULTANT IN DISEASES OF THE HEART, LINCOLN HOSPITAL; CONSULTING
CARDIOLOGIST, SEA VIEW HOSPITAL,

LOUIS FAUGERES BISHOP, JR., M.D.,

ASSOCIATE VISITING PHYSICIAN, BELLEVUE HOSPITAL,

AND

MAX TRUBEK, M.D.,

ASSISTANT VISITING PHYSICIAN, BELLEVUE HOSPITAL,
NEW YORK.

LESIONS of the aortic cusps offering varying degrees of obstruction to the outflowing blood have been, in our experience, a frequent finding; those alterations of less severe degree characterized by thickening with only a moderate degree of calcification at the roots of the semilunar cusps being much more commonly encountered than the advanced stenoses.

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Pathologically, the distorted aortic valves can usually be classified within one of the following etiologic groups:

1. Of infectious origin, including all cases with "rheumatic" type of pathology, and healed bacterial endocarditis.
2. Arteriosclerotic or degenerative lesions without previous inflammation.
3. Congenitally defective cusps with subsequent calcification (Fig. 1).

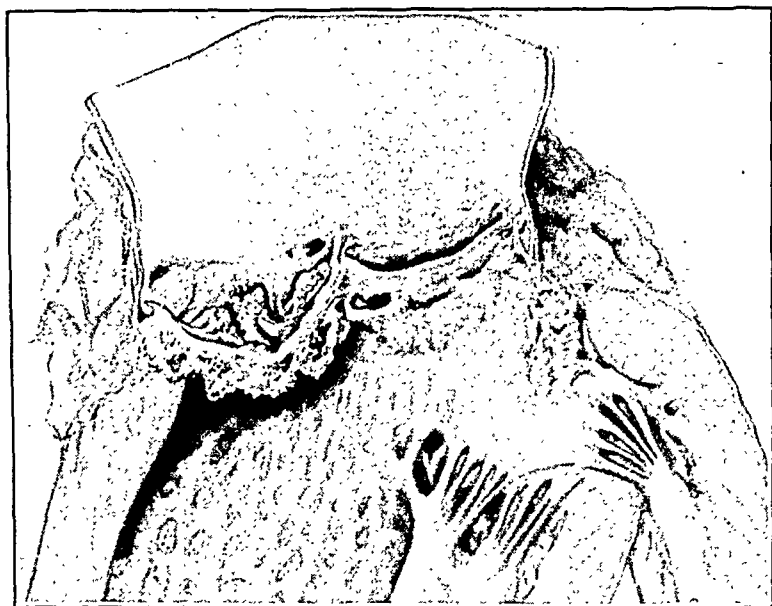


FIG. 1.—Congenital bicuspid aortic valve—aortic stenosis—white male, aged 52. There are two valve cusps and two normal commissures. No raphé within the cusp sinuses. Note uninterrupted swing of free edge of valves. The combined cusp, particularly its free margin, shows extensive calcium deposit.

The age at which the lesion is discovered is not always important for pathologic differentiation. Mönckeberg¹ pointed out that the degenerative process might appear within the aortic ring and annulus fibrosus after the age of 35, almost as a physiologic process. He was of the opinion that the amount of calcium deposited varied with individual predisposition, and that the lesion was often well advanced relatively early in life. These lesions being productive in character, deformities associated with concomitant ulceration usually fall within the other two categories of the above classification. With healing and advanced calcification it often becomes increasingly difficult to decide from gross examination whether we are dealing with the healed stage of an originally inflammatory process or with a defective valve of the bicuspid variety with subsequent calcification (Fig. 2).

The criteria formulated by Sir William Osler² for the gross identification of the bicuspid valve of congenital origin are exceedingly important and in the majority of cases can still be applied. In difficult cases the chief basis for distinction between the bicuspid valve of congenital or inflammatory origin is the relation of the origin of the fibers of the annulus fibrosus to the aortic elastic media at the ridge or raphé dividing the conjoint valve. Using serial sections stained for elastic and connective tissue, Lewis and Grant³ have shown that the congenital raphé is merely an abortive attempt to form a commissure in which the normal arrangement of the aortic layers is deformed but not altered, and that unlike the

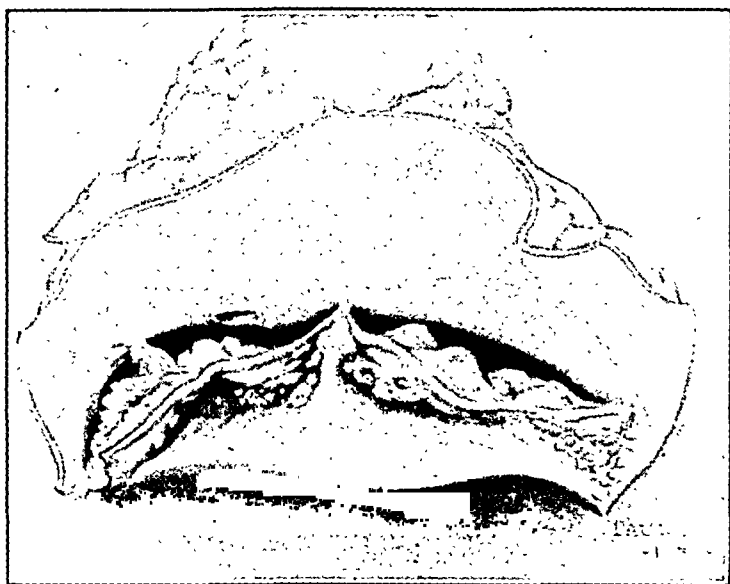


FIG. 2.—Inflammatory (bicuspid) aortic valve showing fused commissure, calcification with aortic stenosis—white male, aged 48. The anterior cusp is divided by a ridge which may be either a fused commissure or a congenital raphé. Such a case of doubtful etiologic nature can be identified by serial section through the questionable ridge.

findings at a normal commissure the relations at the raphé are similar to those found in the center of a normal cusp. However, the fused commissure of old inflammatory origin may present a ridge so shortened and deformed, apparently with two valve cusps of such equal size, that naked eye distinction between such a lesion and a calcified congenital bicuspid valve cannot be made. A case of such a nature occurred in our practice and the study of this specimen, encouraged by Dr. Maude E. Abbott, initiated the present work.

Material and Methods. Nine cases of true congenital bicuspid valves, all except 2 showing a raphé within the sinus, had been

encountered at the Bellevue Hospital morgue during a 2-year period of observation among approximately 5000 autopsies seen through the courtesy of the Office of the Chief Medical Examiner and the Bellevue Hospital Pathological Department. Certain cases of advanced aortic stenosis could not be satisfactorily identified in the gross as to etiology and we undertook the histologic study of this group of specimens. The uncertain cases most often proved to be of inflammatory origin after serial sections through the questionable ridge.

The aortic valves in 12 significant cases were selected for study and differentiation. In those of doubtful nature serial sections, stained for elastic and connective tissue, according to the method of Lewis and Grant,³ were cut either transversely or sagittally through the ridge or raphé dividing the conjoint cusp. A normal valve and commissure and a typical congenital raphé were similarly sectioned for comparison with the pathologic material. The appearance of the valves in the selected cases varied from healthy bicuspid leaflets, with and without a subdividing raphé, to bicuspid valves extensively calcified. From their gross appearance 2 of the cases of aortic stenosis appeared to be calcified congenital bicuspid valves, in one of which there were associated cardiovascular anomalies. A patent ductus arteriosus and coarctation of the aorta suggested that the deformed and calcified valve was a congenitally bicuspid one, but on microscopic examination both cases proved to be bicuspid valves of inflammatory origin. In another specimen, with subacute bacterial endocarditis, serial transverse sections through a low ridge, whose gross appearance was unquestionably that of a congenital raphé within a bicuspid valve showed the normal relationship of the aortic layers imperfectly reversed.

Discussion. In none of our cases of true congenital bicuspid aortic valves did we encounter variation in the number of pulmonary valve cusps or interventricular septal defects. Dr. Maude E. Abbott⁴ has also emphasized the opinion that a congenitally bicuspid aortic valve has in most instances a different developmental etiology than a similar deformity of the pulmonic valve.

The presence of associated cardiovascular anomalies of certain varieties, particularly coarctation of the aorta and patent ductus arteriosus, are considered as important evidence for the congenital (bicuspid) origin of a deformed aortic valve of doubtful nature.^{3,4} Our own case, at first considered a congenital bicuspid valve because of the presence of anomalies, subsequently, on section through the decalcified ridge, showed the typical arrangement of layers as found at a normal commissure. The case of bicuspid aortic valves with bacterial endocarditis conformed in its gross characteristics with a typical congenital defect; the imperfect reversal of layers on microscopic examination of the raphé cannot alter the impression of the congenital nature of this bicuspid valve.

Paget⁵ seems to have been the first to recognize the susceptibility of this type of valve to subsequent thickening or to infection. Many of his bicuspid valves were unknowingly of inflammatory origin. Peacock⁶ reported numerous findings of two aortic cusps but also erroneously included cases of undoubted inflammatory etiology. Osler,² Garrod⁷ and Abbott⁸ have been among the important contributors in calling attention to the frequency with which these anomalous valves become the seat of calcific deposits or of infective endocarditis.

Conclusions. By the method described by Lewis and Grant it was possible to differentiate a congenital raphé or a fused commissure ridge in aortic valves with advanced calcification and stenosis.

The presence of associated cardiovascular anomalies, coarctation of the aorta and patent ductus arteriosus, cannot be taken as presumptive evidence for a congenital defect underlying the calcified aortic cusps.

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A SUCCESSFUL METHOD FOR VACCINATION AGAINST ACUTE ANTERIOR POLIOMYELITIS.*

PRELIMINARY REPORT.

By JOHN A. KOLMER, M.D., D.Sc., LL.D.,

PROFESSOR OF MEDICINE, TEMPLE UNIVERSITY, AND DIRECTOR OF THE RESEARCH
INSTITUTE OF CUTANEOUS MEDICINE,
PHILADELPHIA.

WITH THE ASSISTANCE OF MISS ANNA M. RULE.

(From the Research Institute of Cutaneous Medicine and the Department of Medicine of Temple University.)

WE have recently shown¹ that it is possible to successfully vaccinate *Macacus rhesus* monkeys against acute anterior poliomyelitis by subcutaneous and intracutaneous injections of a vaccine of monkey poliomyelitic cords treated with sodium ricinoleate (Wm. S. Merrell Company). McKinley and Larson² had previously found

* Aided by a grant from the Daniel J. McCarthy Fund for Research in Neurology, Temple University.

that monkeys could be sometimes immunized by intraperitoneal injections of this type of vaccine.*

During the past year we have successfully vaccinated 17 additional monkeys with vaccines prepared as follows:

1. Healthy adult *Macacus rhesus* monkeys, weighing 4 or more kg. of weight, were inoculated intracerebrally (frontal lobe) with 0.2 cc. of a 5% emulsion of monkey poliomyelitic cord (Rockefeller Institute strain) under ether anesthesia.

2. Symptoms of poliomyelitis usually developed in 5 to 9 days and immediately after death, or when the infection was very severe, the hair was sprayed with 5% trichresol solution and the skin over the head and back removed. The cords were then removed under aseptic precautions after the method of removing spinal cords from rabbits in the preparation of rabies vaccine by the original Pasteur method and 8 gm. of a mixture of several cords thoroughly emulsified aseptically in 100 cc. of sterile physiologic saline solution.

3. After fine-mesh filtration under aseptic conditions there was added an equal volume of a sterile 2% solution of sodium ricinoleate in saline solution.†

4. This gave a 4% suspension of mixed tissue in 1% sodium ricinoleate.

5. The mixtures were well mixed and placed in an incubator at 37° C. for 24 hours and then in a refrigerator at 4° to 6° F. for 14 days with daily shaking for a few minutes.

6. Subcultures were made and the vaccines kept in the refrigerator throughout the year. Even though sodium ricinoleate is of low bactericidal activity,³ we have found that the final concentration of 1% is usually sufficient for sterilizing the vaccines when slight contamination had occurred in the removal of some of the cords and the preparation of the emulsions.

Our previous vaccine¹ was a final 1% emulsion of poliomyelitic cord in a 10% solution of sodium ricinoleate, so that the present vaccines were 4 times as strong in virus (4%) with a lower concentration of sodium ricinoleate (1%). Furthermore, the present vaccines were a mixture of several cords in order to better equalize the amount of virus present, as this sometimes varies in individual cords.

Results. 1. Six monkeys were given subcutaneous injections of 0.05 to 1 cc. per kg. every 5 days for 10 injections and 2 additional animals were given 0.1 cc. by intracutaneous injection every 5 days for 10 injections. None developed the slightest clinical evidences of poliomyelitis during the period of immunization and all remained perfectly well. When inoculated intracerebrally with 0.2 cc. of 5% suspension of fresh virus (about 18 minimal infective doses) 1 month after the last dose, none developed the slightest clinical evidences of poliomyelitis, whereas controls inoculated at the same time developed poliomyelitis in 5 to 9 days and succumbed.

2. Seven monkeys were given subcutaneous injections of 0.1 to 1 cc. per kg. every 5 days for 5 injections and 3 additional animals

* We are indebted to Wm. S. Merrell Company for permission to use sodium ricinoleate in the preparation of vaccines (Patent No. 1621118).

† Sterilized by boiling for 10 minutes.

0.1 cc. per kg. by intracutaneous injection every 5 days for 5 doses. None of these animals developed the slightest clinical evidences of poliomyelitis during the period of immunization. When inoculated intracerebrally with 0.2 cc. of 5% suspension of fresh virus 1 month after the last dose, all remained perfectly well except 1 receiving 5 doses of 0.1 cc. per kg. by subcutaneous injection, which developed poliomyelitis 6 days after inoculation progressing to paralysis but surviving. All unvaccinated controls developed poliomyelitis in 5 to 7 days after inoculation.

3. When the vaccinated monkeys were reinoculated intracerebrally 7 months later with 0.2 cc. of 5% suspension of virus, all remained healthy and well and presented no clinical evidences of poliomyelitis. When reinoculated again 3 months later, or about 10 months after vaccination, all but 1 again remained perfectly well and free of all clinical evidences of poliomyelitis so that at this time it may be stated that the immunity has persisted in all but 1 monkey for at least 10 months after vaccination.

These results have shown, therefore, that it is possible to vaccinate *Macacus rhesus* monkeys with 5 injections of sodium ricinoleated vaccine in dose of 0.1 cc. per kg. given every 5 days. The subcutaneous injections of 0.05 cc. per kg. also produced effective immunity. Smaller doses may be likewise effective but so far have not been used. Intracutaneous injections may produce more effective immunity than subcutaneous injections but are too painful, as we know from personal experience (J. A. K.); furthermore, it is likely to be impossible to immunize human beings by this route of immunization unless a larger number of injections are given.

Sodium ricinoleate, however, in the amounts employed, does not completely kill the virus. As previously stated, none of the vaccinated animals showed the slightest evidences of poliomyelitis during or following the period of immunization, but the intracerebral inoculation of monkeys with 0.3 cc. of a vaccine 5 months after its preparation produced mild paralysis about 12 days later and showing thereby the survival of devitalized virus in the vaccine.

All attempts to vaccinate with "dead" vaccines sterilized with heat and various chemical agents by others and ourselves¹ have met with no success. It appears that the vaccine to be effective must contain some living but devitalized virus. Subcutaneous and intracutaneous inoculation of monkeys with a vaccine of fresh virus sometimes produces poliomyelitis and, therefore, cannot be utilized for the vaccination of human beings. Sodium ricinoleate, however, in the amounts employed, appeared to sufficiently devitalize the virus to make subcutaneous and intracutaneous injections entirely safe for the monkeys and yet leaving sufficient virus for engendering effective immunity.

We have taken 0.5, 1.5 and 2 cc. of the vaccine by subcutaneous injection every 5 days. The injections were accompanied by some

stinging pain, especially after the first but less after the second and third injections, which quickly subsided, but there was little or no local reaction except in the 2-cc. doses when the local reactions were comparable to those produced by the subcutaneous injection of rabies vaccine. Fever and constitutional reactions, however, were not produced in us, and, while we have found large doses of sodium ricinoleate by intramuscular injection capable of producing some tissue necrosis in rabbits,³ yet such were not produced in ourselves by even 2-cc. amounts of this poliomyelitis vaccine.

Fortunately for these experiments our blood sera before inoculation were free of antiviral properties, as determined by mixing 0.2 cc. of serum with 0.2 cc. of 5% suspension of virus and injecting the mixture, after standing 2 hours, intracerebrally into 2 monkeys. Both animals developed poliomyelitis in about 7 days.

That the 3 doses of vaccine produced antiviral antibody was shown, however, by repeating the test 2 weeks after the last dose of vaccine, when 2 additional monkeys inoculated intracerebrally with a mixture of 0.2 cc. of serum and 0.2 cc. of 5% suspension of virus allowed to stand for 2 hours, remained perfectly well, whereas a control inoculated with virus alone developed paralysis in 6 days and finally succumbed. These results have shown, therefore, that in the case of ourselves the vaccine was apparently capable of producing antibody for the poliomyelitis virus and probably sufficient for engendering immunity.

It appears to us that this is the only effective method for determining whether or not a vaccine is capable of engendering immunity against poliomyelitis in human beings, because an injection of virus as a test for immunity as done with monkeys is, of course, not permissible, and to vaccinate a group of children to determine over a period of years how many, if any, develop poliomyelitis as controlled by the incidence among a group of unvaccinated individuals would require the immunization of a very large number in the presence of an epidemic. The serum-antiviral test before and after vaccination, however, may be a quicker and more decisive test for acquired immunity, and especially when conducted with children, who are not as likely to have natural antiviral antibody in their sera.

Discussion. We naturally hesitate to advise the subcutaneous injection of a vaccine known to contain some living virus, even though we believe it to be sufficiently devitalized with sodium ricinoleate to make it a safe procedure as determined by the results observed among vaccinated monkeys and ourselves, but we believe that 3 subcutaneous injections of this kind of vaccine at intervals of 5 to 7 days and in dose of from 0.05 to 0.1 cc. per kg. of weight is a safe and effective method for vaccination against acute anterior poliomyelitis.

Indeed, if it is true that human beings acquire immunity to acute anterior poliomyelitis by contact with the virus even without

demonstrable evidences of infection, it would appear that less vaccine may be required per body weight than in the case of monkeys, and especially since less antibody is probably required for the protection of human beings against small amounts of virus entering the upper respiratory tract than required for the protection of monkeys inoculated intracerebrally with 15 to 20 minimal infective doses.

Since these vaccines never produced the slightest evidence of infection in the monkeys and ourselves, and believing that the amount of sodium ricinoleate employed effectively reduces the virulence of the virus, we are at present vaccinating a group of children varying in age from 8 months to 15 years. These have been selected after preliminary antiviral tests with monkeys have shown the absence of antibody in the sera. Three doses are being given at weekly intervals with monkey antiviral tests with the sera of some children after the first and second doses and with the sera of all children after the third dose in order to determine the rapidity of antibody production and the number and size of doses of vaccine required.

The first dose for children under 3 years has been 0.25 cc. and 0.5 cc. for older children up to 15. By making the first dose quite small in this manner and waiting 7 days, opportunity is afforded for antibody production before the second and third doses are administered. Varying amounts are being given in the second and third doses and a subsequent report will soon be made on the results, along with further details on the preparation and standardization of the vaccine. Since the cord of a large-sized monkey will yield about 200 cc. of vaccine, and taking a total of 3 to 4 cc. for the immunization of a child, 1 monkey will yield sufficient vaccine for the immunization of 50 or more children. If subsequent experiments now under way show that it is possible to prepare vaccine of monkey poliomyelitic brain, the yield would be much larger and the cost correspondingly less.

While one may question the importance of vaccination against poliomyelitis in view of the low incidence of the disease, yet I became convinced of its advisability 2 years ago when thoroughly reviewing the situation before commencing these investigations and will present the reasons at the same time.

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POLIOMYELITIS.

A STUDY OF 410 PATIENTS AT THE PHILADELPHIA HOSPITAL
FOR CONTAGIOUS DISEASES.

BY PASCAL F. LUCCHESI, M.D.,

SUPERINTENDENT, PHILADELPHIA HOSPITAL FOR CONTAGIOUS DISEASES,
PHILADELPHIA, PA.

DURING the summer of 1932, Philadelphia experienced its second epidemic of poliomyelitis. The greatest portion of the reported cases was sent to this hospital for diagnosis and treatment. Four hundred and ten persons suspected of having fallen victims to this dreaded disease were sent to us between the months of July and November. It is not necessary to mention that all were not cases of poliomyelitis. As is common during an epidemic, some patients are wrongly but justifiably suspected.

From the outset we were confronted with the problem of abortive poliomyelitis. What cases should be and what cases should not be diagnosed as such? Were we justified in venturing such a diagnosis from a hospital viewpoint? After careful consideration it was deemed advisable not to make this diagnosis, as the margin of accuracy was too narrow. Accordingly no patient was discharged from this hospital as one of abortive poliomyelitis, although, to be sure, many cases might have been designated as such. The diagnosis of poliomyelitis was only made when the patient presented the accepted clinical and pathologic picture. Positive spinal fluid findings were obtained in most cases. The patient was discharged with a diagnosis of poliomyelitis with or without paralysis. It was found difficult in some cases, especially infants, accurately to determine the presence or degree of weakness or paralysis.

Routine. On admission, patients were examined, spinal puncture was performed, the fluid immediately studied and treatment instituted. Doubtful cases were isolated until a definite diagnosis could be made. Immune serum was given to all patients in whom it was felt that an active progressive infection was present, irrespective of the presence or absence of paralysis. Patients with definite evidence of paralysis, but without evidence of progress or extension of paralysis, were not given immune serum. The immune sera consisted of convalescent and contact serum. Whole blood was also used. The last 2 were given intramuscularly, the former intravenously. It was attempted to give a total of 100 cc. of immune serum divided into 40 cc. of convalescent and 60 cc. of contact. We did not have a control group.

Two respirators were in constant use throughout the epidemic. At times, because of this limited number of respirators, it was

necessary to transfer patients to other hospitals for treatment. In this way, 8 of our patients were treated by neighboring hospitals. These are not included in this study.

Quarantine. It was not thought necessary to keep patients in this hospital for 21 days. Of course, some were kept the full time, either because of the severity of the illness, or because of the lack of proper home facilities. The majority of patients were detained between 10 and 15 days. The average number of hospital days for the entire group was 10.6. When the temperature, pulse and respirations were normal for about 7 days, and there was no evidence of extension of paralysis, patients were transferred to their homes in our ambulances. The balance of the quarantine period was then maintained at home. As far as we can determine, no secondary cases were experienced because of this practice.

TABLE 1.—DIFFERENTIAL DIAGNOSIS OF 410 CASES REFERRED AS POLIOMYELITIS.

	No. of cases.	Percentage of total.
Poliomyelitis	304	74.1
La grippe	31	7.6
Gastro-intestinal upset	16	3.9
Tonsillitis	13	3.2
Bronchopneumonia	6	1.5
Lobar pneumonia	6	1.5
No disease	3	0.7
Bronchitis	2	0.5
Localized meningitis	2	0.5
Acute pharyngitis	1	0.2
Tracheobronchitis	1	0.2
Rheumatic fever and rheumatic endocarditis	1	0.2
Scarlet fever	1	0.2
Rheumatoid arthritis	1	0.2
Catarrhal jaundice	1	0.2
Hysteria	1	0.2
Pulmonary tuberculosis and tuberculous meningitis	1	0.2
Typhoid fever	1	0.2
Arthritis of hip	1	0.2
Influenzal meningitis	1	0.2
Cerebrospinal meningitis	1	0.2
Acute peritonitis and ruptured diverticulitis	1	0.2
Food allergy	1	0.2
Anterior spinal thrombosis	1	0.2
Acute arthritis	1	0.2
Chorea	1	0.2
Poison ivy	1	0.2
Drug rash	1	0.2
Alcoholism	1	0.2
Pyelitis	1	0.2
Acute otitis media	1	0.2
Scurvy and rickets	1	0.2
Acute sinusitis	1	0.2
Vincent's angina	1	0.2
Tuberculous meningitis	1	0.2

In all, 410 patients were admitted as suspected cases of poliomyelitis. This diagnosis was confirmed in 304 (74.1%). In 106 (25.9%) this diagnosis was disproved. No doubt, as can be seen in Table 1, the diagnosis in some of these cases might be disputed.

Some could have easily fitted into the picture of the so-called abortive type of poliomyelitis; but in the majority of cases the diagnosis was clear-cut. The difficulty attending a diagnosis of abortive poliomyelitis is admitted by all physicians. Indeed, in a study of 446 cases of suspected poliomyelitis referred to the Herman-Kiefer Hospital in Detroit, Gordon¹ could only verify this diagnosis in 50.2% of this number.

Age, Sex, Race. In all, 304 cases of poliomyelitis were treated, ranging in age from 4 months to 52 years. Twelve (5.6%) were under 1 year. The youngest patient was a female child, aged 4 months. The ratio of male to female was equal in this age group. The largest number of patients fell in the age group of 0 to 4 years, inclusive. This formed 47.7%. In other words, 53.3% of those affected were children under 5. These figures correspond to the unpublished age-group figures of the New York City epidemic of 1931.² The next highest number of cases occurred in the 5 to 9 years group, representing 27.6%. The small number of 1.3% represents the 20 years or more age group. As to the ratio of male to female, the male group predominated 188 to 116.

TABLE 2.—PERCENTAGE DISTRIBUTION BY AGE GROUPS.

	Cases, 304 Per cent.
Under 1 yr.	5.6
0 to 4 yrs.	47.7
5 to 9 "	27.6
10 to 14 "	13.2
15 to 19 "	4.6
20+ "	1.3

TABLE 3.—AGE AND SEX INCIDENCE.

	Male.	Female.	Ratio: Males to 1 female.
Under 6 mos.	2	
6 mos. to 1 yr.	9	6	1.50
12 mos. to 1½ yrs.	14	7	2.00
18 mos. to 2 "	34	18	1.89
3 yrs.	18	14	1.29
4 "	22	18	1.22
5 "	12	7	1.71
6 "	15	10	1.50
7 "	11	8	1.38
8 "	8	5	1.60
9 "	6	2	3.00
10 "	6	4	1.50
11 "	4	2	1.50
12 "	7	4	1.75
13 "	6	3	2.00
14 "	3	1	3.00
15 "	1		
16 "	2	1	2.00
17 "	1	1	1.00
18 "	3	1	3.00
19 "	2	2	1.00
20 to 24 yrs.	3		

It was noted that as the epidemic progressed into the months of September and October, patients ranging in the group of 5 to 9 years predominated, while in the early months of the outbreak the age group of 0 to 4 years was prevalent.

The race study shows a remarkable increase among negroes in comparison with the 1916 epidemic. This is undoubtedly due to the tremendous increase in the negro population in Philadelphia since the 1910 census. In 1910, the total population of this city was given as 1,724,630. Of this number, there were 84,459 blacks (4.89%). In the census of 1930, with a total city population of 1,978,879, there were 219,599 blacks (11.09%). The actual increase in the colored population in Philadelphia from 1910 to 1930 is 135,140 (160%). However, if we consider the percentage of whites to blacks, we will find that the percentage increase of blacks is 6.2%. The number of poliomyelitis patients among the blacks admitted to this hospital in 1916 is 2.9%; whereas in 1932 it was 15.5%. This shows an increase of 12.6% of blacks contracting poliomyelitis, in comparison to an increase of 6.2% population. Undoubtedly, there was a greater percentage of susceptibles among the blacks, for it is interesting to note that of the total increase of 254,249 in the total population of Philadelphia from 1910 to 1930, 135,140 (53.5%) were black.

Symptomatology. The information recorded with reference to the onset of the present illness and the history of past diseases was obtained by the ambulance nurse from parents in most cases. It is needless to say that in some instances this information was given inaccurately. The correctness of the data obtained in this respect is in direct proportion to the intelligence of the parents and the ability of the questioner to elicit the information. In most cases, parents were found to be good observers, but in a small number their observations were inaccurate. However, we feel that a fairly good picture can be drawn from the information on hand.

The usual order of symptoms—fever, vomiting and headache—prevailed in the majority of patients admitted. As will be seen in Table 4, fever marked the onset of poliomyelitis in the majority of cases, nausea, or vomiting and headache ranging second and third, respectively. Among the less common symptoms of onset, drowsiness was the leader.

The most prevalent physical sign observed was the absence of knee jerks. Superficial and deep reflexes were next in order. Rigidity or stiffness of the neck was present among a goodly portion. These percentages may seem slightly high, but it must be remembered that about 50% of the patients showed on admission some signs of weakness or paralysis.

As mentioned above, 304 patients were discharged with a diagnosis of poliomyelitis. Of this number, 192 (63.2%) showed some evidence of weakness or paralysis. The distribution of paralysis

in this group was mostly centered in one extremity, either the arm or leg, with paralysis of both extremities next most common.

TABLE 4.—INCIDENCE OF SIGNS AND SYMPTOMS.

	Per cent.
Fever	81.58
Nausea and vomiting	52.63
Headache	48.68
Drowsiness	21.05
Hyperesthesia	7.89
Irritability	6.91
Excessive sweating	5.59
Sore throat	5.59
Apprehensiveness	3.94
Restlessness	3.94
Constipation	2.63
Diarrhea	2.24
Coryza	1.64
Knee jerks	Absent 53.32
Superficial reflexes	Absent 49.68
Deep reflexes	Absent 47.04
Stiffness of neck	Present 40.13
Kernig	Present 22.37
Babinski	Present 10.86
Muscular twitching	Present 5.26
Spine sign	Present 3.62
Muscular tremor	Present 2.96

TABLE 5.—DISTRIBUTION OF PARALYSIS.

Both legs	29
One leg	64
Both legs and both arms	11
Both legs and one arm	8
One arm	33
One arm and one leg (same side)	4
One arm and one leg (opposite side)	0
Both arms	12
Both arms and one leg	3
Trunk	9
Facial alone	16
Throat or neck	3
Total	192

Etiology. It was attempted to determine what part the occurrence of other acute infections played toward the production of immunity against poliomyelitis; whether the absence or presence of tonsils makes one more susceptible; and if vaccination against small-pox or diphtheria prophylaxis increases the resistance of a child to poliomyelitis. A résumé of the history in each case shows that 64.1% of the poliomyelitis patients suffered from one or more attacks of the acute infections of childhood. Tonsils were present in 81.6% of the group of cases. It was not noted whether the tonsils presented evidence of disease. Amoss and Taylor³ have shown that the healthy nasopharynx furnishes virucidal substances. From their observation we may assume that the nasopharynx was diseased in this group of patients; 56.3% had been vaccinated

against smallpox and 51.3% had toxin-antitoxin prophylaxis against diphtheria.

Laboratory Data. Spinal fluid examinations showed the usual findings. The fluid was clear in color, under increased pressure in most cases. A fibrin web formed, upon standing, in a small number of cases. The average cell count was 93 leukocytes, the lowest 2 and the highest 1067. The predominating type of cell was the lymphocyte.

Treatment. In the absence of any definite specific for the treatment of poliomyelitis, convalescent and contact serum was used. The majority of patients were given serum on admission. A smaller group of patients, who presented definite evidence of paralysis, or in whom there was great doubt as to the presence of poliomyelitis, were not given serum. Of the 304 cases of poliomyelitis, 254 (83.55%) received serum; 50 (16.45%) did not. Among those who received serum (254), 124 presented evidence of weakness or paralysis on admission; 130 did not. Eighty-five of those showing evidence of weakness or paralysis (124), and 96 of those showing no evidence of weakness or paralysis (130) were admitted during the first 4 days of the disease. On discharge it was found that 154 (60.63%) of those receiving serum showed evidence of weakness or paralysis, an increase of 30 patients. Of the 50 who did not receive serum, 28 showed evidence of weakness or paralysis and 22 did not. Ten of the former and 14 of the latter were admitted during the first 4 days of the disease. On discharge, 38 showed evidence of weakness or paralysis and 12 did not.

TABLE 6.—DATA ON SERUM TREATMENT, PARALYSIS, MORTALITY.

Day of disease.	No. of cases in group.	Serum.				No serum.				Died.	
		Weakness or paralysis.		No weakness or paralysis.		Weakness or paralysis.		No weakness or paralysis.		Serum.	No serum.
		On admission.	On discharge.	On admission.	On discharge.	On admission.	On discharge.	On admission.	On discharge.		
1 . . .	61	16	22	37	31	2	3	6	5	4	0
2 . . .	45	20	25	20	15	2	4	3	1	2	1
3 . . .	54	24	32	23	15	3	5	4	2	4	2
4 . . .	45	25	27	16	14	3	4	1	0	3	0
5 . . .	34	10	13	15	12	6	7	3	2	1	0
6 . . .	23	9	12	8	5	5	6	1	0	0	2
7 . . .	16	8	11	5	2	3	3	1	0	0	1
8 . . .	10	4	3	1	2	3	3	2	2	2	0
9 . . .	1	0	0	1	1	0	0	0	0	1	0
10 . . .	3	2	2	0	0	0	1	1	0	0	0
11 . . .	2	0	0	0	0	2	2	0	0	0	0
12 . . .	2	2	2	0	0	0	0	0	0	0	0
13 . . .	1	1	1	0	0	0	0	0	0	1	0
14 . . .	2	0	0	2	2	0	0	0	0	0	0
15 . . .	2	2	2	0	0	0	0	0	0	0	0
? . . .	3	1	2	2	2	0	0	0	0	0	0
	304	124	154	130	100	28	38	22	12	18	6

In all, there were 192 (63.2%) cases with evidence of weakness or paralysis, while 112 (36.8%) showed no evidence of paralysis.

There occurred 24 deaths, a percentage death rate of 7.89. Of the 24 patients who died, 18 received serum and 6 did not; 22 (91.67%) patients died within the first week of their disease. Two (8.33%) died within the second week.

TABLE 7.—DEATHS FROM POLIOMYELITIS BY DAY OF DISEASE.

	Deaths.	Per cent.
First day	3	
Second day	4	
Third day	6	
Fourth day	3	
Fifth day	1	
Sixth day	2	
Seventh day	3	
First week	22	91.67
Second week	2	8.33
Total	24	

TABLE 8.—SUMMARY OF DATA ON SERUM THERAPY AND RESULTS.

	Serum.	No serum.
Admitted with paralysis	124	28
Died	11	6
Admitted without paralysis	130	22
Died	7	0

Of the 24 patients who died, 17 required the use of the respirator; 10 of the 17 succumbed despite the use of respirator; 7 recovered from respiratory paralysis but subsequently died. The respirator was a great aid in relieving those with evidence of transitory paralysis. Patients who required the respirator longer than 72 hours did not fare well. Several patients recovered after several days in the respirator. However, investigation shows that these patients died later of some other disease. A careful check-up is being made on these patients at present.

TABLE 9.—SUMMARY OF DATA.

Total No. of cases.	Total paralysis.		Serum treated.			No serum.			Deaths.			Mort., per cent.
			Paralysis.		Total.	Paralysis.		Total.	Serum.		Total.	
	Yes.	No.	Yes.	No.		Yes.	No.		Yes.	No.		
304	192	112	154	100	254	38	12	50	18	6	24	7.89

Summary. 1. During the summer and fall of 1932, 410 patients were admitted to this hospital as suspected cases of acute anterior poliomyelitis. The diagnosis was verified in 304 (74.1%).

2. The majority of those affected were in the age groups of 0 to 4 years and 5 to 9 years, 53.3% in the former and 27.6% in the latter. There were 188 males and 116 females. As to race, 84.5% were whites and 15.15% were negroes.

3. Two hundred and fifty-four patients (83.5%) received serum; 124 of these showed evidence of weakness or paralysis on admission. Upon discharge from the hospital this number increased to 154.

4. Fifty patients (16.5%) received no serum on admission. Of this number, 28 showed evidence of weakness or paralysis. Upon discharge this number increased to 38.

5. One hundred and ninety-two (63.2%) of the patients were discharged with evidence of paralysis; whereas on admission 152 (50%) presented such evidence.

6. There occurred 24 deaths (7.89%). Eighteen of this number received serum; 22 of the deaths occurred within the first week of the disease, 2 in the second week.

7. Of the 24 fatal cases, 17 required the use of the respirator; 10 of this number died while in the respirator.

Conclusion. In view of the above findings, the conclusion seems justified that convalescent serum was of little value in the prevention of paralysis.

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ENCEPHALITIS IN CHILDREN APPARENTLY CONGENITAL AND FOLLOWING MATERNAL INFLUENZA.

BY WINIFRED BAYARD STEWART, A.M., M.D.,

ASSISTANT CLINICAL PROFESSOR OF NEUROLOGY, WOMAN'S MEDICAL COLLEGE OF PENNSYLVANIA; INSTRUCTOR IN NEUROLOGY, MEDICAL SCHOOL AND GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA; ASSISTANT NEUROLOGIST, PHILADELPHIA GENERAL HOSPITAL, PHILADELPHIA, PA.

INFLUENZA is recognized as being one of the most serious infections which may complicate pregnancy. Miscarriages, abortions, and premature labor are frequently induced by an attack of this disease and the mortality rate is definitely higher in pregnant than in non-pregnant women. Jordan¹ concludes, after an extensive review of the literature, that an attack of influenza is more serious in the later than in the earlier months of pregnancy; that severe influenza is more likely to cause interruption of pregnancy than a mild attack of the disease, while the mortality rate is higher in those cases in which the pregnancy has been interrupted.

Death of the fetus is a frequent, but not invariable result of maternal influenza. Welz² reported a fetal mortality of 66 per cent in his series of 21 cases, and noted that fetal mortality is lessened when the mother recovers. This high fetal mortality rate has been variously ascribed to premature delivery, to toxemia, to hyperpyrexia, to anoxemia, and to direct infection through the placenta.

Very few reports of autopsies on these infants can be found, however, and none includes an examination of the central nervous system. Abt³ reported a 2 weeks' premature infant born of a woman suffering with influenza, who at birth presented signs of an upper respiratory infection with râles in the chest and cyanosis. It died on the third day. Pathologic examination revealed hemorrhagic bronchopneumonia and septic endocarditis. Streptococci were present in all organs examined. Townsend's⁴ case was a 2 weeks' premature infant who had signs of influenza at birth, the mother having developed the disease 1 week prior to labor. Two cases of bronchopneumonia, developing 18 to 24 hours after delivery of mothers suffering with influenza, were reported by Woolston and Conly.⁵

Kosmak,⁶ in a series of 21 cases of maternal influenza, reported that 3 children were born alive and died postpartum, 1 was stillborn, and 3 were aborted after the 5th month, while 2 mothers died undelivered. He also observed that many of the surviving infants were definitely below par. Other than this, however, it does not appear that any observations have been made concerning the subsequent health and development of the children.

Fortunately, in the literature on epidemic encephalitis complicating pregnancy, more statistics are available regarding the subsequent history of living children and on autopsy findings of the dead infants. This disease is not so fatal to the pregnant woman or the fetus as is influenza. However, fetal deaths have occurred, and in several the postmortem findings showed changes characteristic of epidemic encephalitis. In Marinesco's case,⁷ a classical one of this kind, the mother died of epidemic encephalitis about 3 months before term after an illness of 3 weeks. The death of the fetus took place a day before that of the mother, as evidenced by absence of fetal movements and heart sounds. Pathologic examination of the brains of both mother and child revealed the typical perivascular cuffing characteristic of epidemic encephalitis. A similar case was reported by Kononowa.⁸ Santi⁹ and Balaban¹⁰ each reported a case of epidemic encephalitis in an infant born of a mother who was suffering with this disease. In each case, autopsy findings confirmed the clinical diagnosis. These 2 cases, however, might have been owing to contact.

Symptoms of epidemic encephalitis have been observed to develop in infants nursed by mothers attacked with encephalitis, by Hallé,¹¹ and also by Klippel and Baruk.¹² The autopsy of Hallé's infant

revealed no evidence suggestive of epidemic encephalitis, however, while the one reported by Klippel and Baruk recovered.

Roques¹³ considers three possible modes of infection from mother to child: (1) by direct contact; (2) through the milk, or, (3) by transplacental passage of the virus, which he favors as being the most probable. This route of infection has some experimental confirmation in that Levaditi, Harvier, and Nicolau¹⁴ demonstrated that the virus obtained from encephalitis in man, can, when inoculated into rabbits, pass through the placenta and localize the fetal nervous system. The cases cited by Marinesco and Kononowa appear to be good evidence in support of this mode of transmission. Thus there seems to be definite evidence that both in the case of influenza and of epidemic encephalitis, transmission from the mother to the child can occur.

The case reports here presented are of interest, not only because the children appear to have congenital encephalitis, but also because they were born of mothers suffering with influenza in the later months of pregnancy. None of these women had symptoms suggestive of epidemic encephalitis. All of them survived the disease and, as far as can be determined, none shows any signs of the sequelæ of encephalitis. The children, on the other hand, show character defects typical of postencephalitic behavior change, and in 5 cases there is evidence of organic involvement of the extrapyramidal system.

Case Abstracts. CASE 1.—E. H., white female, born February 1, 1919. The mother had influenza in the 8th month of pregnancy and was delivered of twins at term. One child died at the age of 6 months of "malnutrition." No details concerning her physical condition can be obtained. The case reported is the surviving twin. She had measles and diphtheria, but no other acute illnesses in childhood. The mother states that she has been hyperactive since infancy. She was slow in learning to talk, seemed somewhat mentally retarded, and has always been a serious behavior problem. She was referred to the Graduate Hospital in 1930 for study. Physical examination revealed that she was small and underdeveloped for her age, with mild choreiform tremors. Neurologic examination was otherwise negative. Her I. Q. was 38, but because of her great distractibility this estimate was not considered to be entirely accurate. When seen in April, 1934, her tremors were much more severe and she had a marked dysarthria. Otherwise, her neurologic examination was negative. She is hyperactive, hypersexed, destructive, and vicious. The Wassermann test is negative. Six siblings are apparently normal. The diagnosis of congenital encephalitis was made in this case because the symptoms apparently started at birth and have been progressive. Aside from measles and diphtheria the child has suffered from no acute illness.

CASE 2.—R. C., white male, born October 22, 1918. During his mother's severe attack of influenza, the child was born about 2 months premature. The delivery was otherwise uncomplicated. At 3 weeks, the child had severe convulsions, the cause of which was undetermined. As an infant he was delicate and seemed rather stiff. He sat up at 2 years, talked at 4, and walked at 5. He had measles, mumps, and varicella, but no other acute infections. He was referred to the Graduate Hospital in May, 1930. He

was hyperactive, and at the same time tired very easily. He had a marked rigidity of the extrapyramidal type. Tendon reflexes were all hyperactive, but there were no pathologic reflexes. Arm swing was absent on the right and diminished on the left. There was a marked hypersalivation. His I. Q. was 79. The Wassermann test was negative. His mother complained that he was hard to manage and had severe temper tantrums when crossed. The diagnosis of congenital encephalitis was made because of the marked symptoms of a lesion of the extrapyramidal system which has apparently existed since birth.

CASE 3.—H. M., a negress, born September 19, 1918. Her mother had influenza at the time of delivery. The child is said to have been born with a "cold" which lasted several weeks. She had measles, mumps, pertussis, and varicella in childhood. Although she developed normally, she was abnormally hyperactive, and has been a serious behavior problem since early childhood. She was referred to the Philadelphia General Hospital for study in 1930 because of her conduct disorder. Physical examination revealed a well-developed but hyperactive child. She had impairment in automatic associated movements, with some rigidity and tremor of the left hand. Tendon reflexes were greater on the left than on the right. Her I. Q. was 80. The Wassermann test was negative. As she grew older, her delinquencies became more serious. Her behavior is of the compulsive type. She is very hyperactive and noisy. She hits and pinches other children. She is immoral. She was finally committed to Byberry in September, 1933, where she causes a great deal of disturbance. Of 5 siblings, 4 are well adjusted. One brother has had some character change following a severe cerebral concussion in 1930. The characteristic behavior change, as well as the signs of organic involvement of the extrapyramidal system, led to the diagnosis of encephalitis in this case. The absence of any symptoms of an acute infection of this nature other than the "cold" she had at birth suggests that the condition is congenital.

CASE 4.—E. E., white male, born October 12, 1918. The mother had a slight attack of influenza during the 8th month of pregnancy, from which she entirely recovered. The delivery was normal, but the child did not cry for 24 hours after birth, following which he cried almost incessantly during the first 5 months of life. At 6 months, he had a severe attack of diarrhea, which lasted for several weeks. Aside from this, measles was the only other disease in childhood. He has always been weak on the left side of his body and in addition has been very hyperactive. He was referred to the Graduate Hospital for study in December, 1929. Physical examination revealed marked arrhythmia of winking and rigidity of muscles of the right face, arm, and leg of the extrapyramidal type. Reflexes were greater on the right than on the left, but no pathologic reflexes could be demonstrated. He also had a mild dysarthria and loss of automatic associated movements of the right side. He showed a marked character disorder. He could not be controlled in school, hit other children, and had violent temper tantrums. When last seen in March, 1934, his father asked that he be committed to Byberry, as he feared that he might do harm to the other children in the family. He is of normal intelligence. Four siblings are normal and well behaved. This case is clearly one of encephalitis and is apparently congenital.

CASE 5.—A. L., white male, born October 1, 1918. The mother had just recovered from a severe attack of influenza when she fell into labor 1 month before term. The delivery was normal. The child seemed fairly normal at birth, but had several convulsions a few days after. He was slow in developing. He walked at 3 years and talked at 5. He had measles, varicella, and bronchitis in childhood. He was examined at the Philadelphia General Hospital in 1930, and again in 1934. Physical examination showed

some loss of automatic associated movements, asymmetry of finger spacing, slight rigidity of the cog-wheel type, and a marked dysarthria. He was otherwise neurologically negative. He is definitely feeble-minded, having an I. Q. of 30. The Wassermann test was negative. A diagnosis of encephalitis was made in this case on the basis of the neurologic findings. It is apparently congenital.

CASE 6.—T. K., white male, born July 20, 1923. The mother had a severe attack of influenza at the time of the child's birth. The delivery was normal but she states that her physician told her that the child was born with a "sleeping brain." The child was very lethargic during the first few months of life, and was very slow in learning to walk and talk. He had measles, varicella, pertussis, and pneumonia in childhood. He was referred to the Graduate Hospital for study in 1928, at which time, he was hyperactive, was unclean in his personal habits and had violent temper tantrums when crossed. Neurologic examination was negative with the exception that his pupils reacted to light but not to accommodation. His I. Q. was 90, and the Wassermann test negative. He is now in an orphanage, where he seems to be making a fairly good adjustment. The history of somnolence, dating from birth, the reverse Argyll-Robertson pupil, a common finding in epidemic encephalitis, and the behavior disorder, led to the diagnosis of congenital encephalitis.

CASE 7.—C. H., white male, born April 21, 1919. The mother had influenza in the 7th month of pregnancy, from which she fully recovered and had a normal delivery at term. The child was slow in developing. He walked at 19 months, and talked at 3 years, at which time he had a distinct impediment in speech. He had measles, varicella, and bronchitis in childhood. Since infancy, he has been hyperactive and difficult to control. He was brought to the Philadelphia General Hospital in December, 1927, by his mother, who said she could not manage him. He had taken \$8 from her pocketbook, treated the boys in the neighborhood to candy, bought 12 toy balloons and stayed out all night. The delivery man found him in a bread box in front of a grocery store the following morning. Physical examination revealed a very hyperactive boy of 9 years, showing no physical abnormalities. Since then, he has had a long court record. He has stolen many bicycles, which he rides for a while, and then abandons. He is a run-away, and has made physical attacks on several people. He was committed to Glen Mills in 1931 for breaking into a store. He escaped 2 weeks afterward, and has not been heard from since. There are 4 siblings, all apparently normal.

All of these cases have several important features in common. They were born of mothers who had influenza during the later months of pregnancy. Their symptoms have apparently existed from the time of birth. They give no history of acute illness, which might have been epidemic encephalitis, nor in any case did the onset of symptoms coincide with the occurrence of one of the usual diseases of childhood.

In spite of the fact that no corroborative autopsy evidence can be offered, there is little doubt as to the diagnosis in these cases. In 5 there is sufficient evidence of organic involvement of the extrapyramidal system to verify the diagnosis of encephalitic sequelæ. Four are Parkinsonian in type, while the 5th has choreiform tremors, which are increasing in severity. The 6th case gives a definite

history of lethargy which was first noticed at birth. In addition, examination of his pupils revealed the reverse Argyll-Robertson phenomenon, which is recognized as being a common sequel of epidemic encephalitis. The 7th was the only case in which the physical findings were negative. Here, the diagnosis was based on the type of behavior disorder.

Postencephalitic behavior, like the behavior seen frequently following cerebral concussions and in a milder form complicating Sydenham's chorea, is definitely compulsive in type. It seems to be owing to lack of inhibition rather than to willful antisocial tendencies. These individuals are seized by uncontrollable impulses which they are compelled to follow and afterward are at a loss to explain. All of the children, except A. L., who is an imbecile, show this characteristic type of behavior, while C. E., unhampered by physical infirmities, is the best illustration of it.

The majority of these cases, therefore, present both the behavior disorder as well as the organic signs characteristic of the sequelæ of epidemic encephalitis. They appear to be congenital and follow maternal influenza.

The possibility of a relationship between influenza and epidemic encephalitis has been implied by some clinical evidence. The coincidence of the two recent epidemics, the definite encephalitic symptoms, such as somnolence and diplopia, which sometimes accompany an attack of influenza, and the occurrence of clear-cut cases of encephalitis during epidemics of influenza, suggest the kinship of these two diseases. It is also a well recognized fact that many individuals presenting unmistakable signs of chronic encephalitis give a definite history of having had influenza, but, on the other hand, have never had symptoms suggestive of acute encephalitis. However, it must be added that it is not always possible to obtain a history of either infection in these cases. In addition, there is some bacteriologic evidence that the influenza bacillus may be the etiologic factor in epidemic encephalitis. The work of Crofton,¹⁵ as well as that of the writer in collaboration with Evans,¹⁶ strongly suggests this hypothesis. Since the 1918 epidemic, however, the Pfeiffer bacillus has fallen into abeyance as the sole causal factor in influenza.

While the cases cited in this report cannot be accepted as proof of the existence of a common etiologic factor in these two diseases, they suggest that such may be the case. While keeping in mind the possibility of the *post hoc ergo propter hoc* fallacy in these cases, it is worth while to investigate the prenatal histories of children showing signs of chronic encephalitis, not preceded by an acute attack of the disease. In all cases of fetal death, as a result of maternal influenza, the autopsy should include an examination of the central nervous system.

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INSULIN ALLERGY. TREATMENT WITH HISTAMIN.

BY WILLIAM S. COLLENS, B.S., M.D.,
CHIEF OF DIABETIC CLINIC,

GEORGE LERNER, M.A., M.D.,
ASSISTANT OF DIABETIC CLINIC,

AND

SOLOMON M. FIALKA, M.D.,
ASSISTANT OF DIABETIC CLINIC, ISRAEL ZION HOSPITAL,
BROOKLYN, N. Y.

(From the Diabetic Clinic, Israel Zion Hospital.)

SINCE the introduction of insulin into the therapy of diabetes, it has been observed that a certain percentage of these insulin-treated cases develop either reactions at the site of injection, or general reactions which are quite characteristic of protein sensitization. The literature of the past 10 years contains a number of reports of insulin-treated patients who developed these allergic reactions. A complete review of this subject up to 1932 is found in an article on insulin allergy by Allan and Scherer.¹ An excellent study of the immunologic considerations of insulin hypersensitiveness was made by Tuft.²

When a diabetic patient on insulin treatment develops a protein reaction, the problem becomes a very disconcerting one, particularly if the diabetes is so severe that its management and control require the continued use of insulin. The incidence of patients experiencing sensitization reactions, among insulin-treated cases, is a significant one. Allan and Scherer report it as high as 14.1% in a collected series of over 1800 diabetics. Lawrence,³ in 1925, observed these

reactions in as many as 30% of his cases. We have collected 407 cases of insulin-treated diabetics in the past 3 years and have found 30 patients who developed protein reactions, an incidence of 7.3%.

Although there have been sporadic case reports of generalized urticarial reactions,² all of our cases gave only local reactions. Of the 30 cases in our series, 27 showed local reactions beginning between the 7th and 15th day after insulin therapy was instituted. Three cases developed reactions after 3 weeks of treatment. The reactions were uniformly characteristic in all cases, and differed only in degrees of severity. They were characterized by the development, between 1 and 6 hours after the injection, of a localized swelling, redness, heat, surrounding erythema, severe itching and pain at the site of injection. These reactions would last, in some cases, as long as 36 hours and then subside spontaneously. The symptoms would frequently become so distressing that some means had to be found to relieve the patients. Just as with other observers, our experience has been that merely changing the commercial type of insulin used was sufficient to make a continuation of the treatment possible. Twenty-five patients responded to this form of treatment. Five patients showed reactions to all types of insulin, so that it became imperative that diabetic treatment be continued with dietetic restrictions alone (Table 1).

Attempts at desensitization have frequently been employed and sometimes successfully. We have used this procedure with 2 patients who showed positive skin tests to all types of insulin, including crystalline insulin. Desensitization, with commercial Lilly insulin, was started in both cases with 0.0001 unit and gradually increased by doubling the dose every other day. When 0.1 unit was reached, the dose was increased by tenths of a unit. The procedure was necessarily long and covered a period of 3 months. At the end of this period, both patients were able to tolerate as much as 15 units in a dose, given twice a day. Desensitization, however, lasted only for 1 month. Both patients again began to show local reactions so that it became necessary to stop the insulin. One year later 1 of these patients experienced an infection of a foot with a severe break in sugar tolerance. Insulin therapy was indicated and employed with the development of such mild local reactions that it was possible to continue using it.

Spontaneous desensitization has been reported in a few cases of insulin allergy. Sturtevant,⁴ in 1924, reported a case of a diabetic patient who developed a local, hard, painful nodule at the site of injection. The skin over the nodule was hot to the touch, red, raised and clearly marked off from the normal skin. The reaction lasted 72 hours and then gradually disappeared. These lesions appeared after every injection for 6 weeks, then became less severe and soon disappeared completely, so that the patient was able to take insulin without any discomfort. Lasersohn,⁵ in 1930, reported

a case of a patient who developed a local reaction at the site of injection. After 3 weeks, the local reaction was less marked, and in another week had entirely disappeared.

TABLE 1.—RESULTS OF TREATMENT IN 30 DIABETICS WITH LOCAL INSULIN REACTIONS.

Name.	Type of reaction.	Onset of reaction, No. of days after beginning insulin.	Type of insulin to which patient was sensitive.	Treatment.	Results.
J. A.	Local	14	Lilly	Histamin	Good.
L. A.	Local	24	Lilly	Special	Relieved; able to take regular insulin in 9 mos.
S. A.	Local	10	Stearns	Special	Relieved.
D. B.	Local	10	Lilly	Special	Relieved.
S. C.	Local	15	Lilly	All brands insulin	Sensitive; insulin discontinued.
L. D.	Local	15	Stearns	Special	Relieved.
B. D.	Local	8	Squibb	Special	Relieved.
M. D.	Local	11	Lilly	All brands insulin	Sensitive; insulin discontinued.
S. E.	Local	10	Lilly	Special	Relieved.
R. E.	Local	9	Lilly, Lilly Spec. and Mulford	Squibb	Relieved.
F.	Local	10	Squibb	Special	Relieved.
R. F.	Local	11	Lilly	Lilly Spec., Hog, Mulford	Relief in 2 mos.
S. F.	Local	..	Stearns	Special	Relieved.
H. G.	Local	10	Lilly	Special	Relieved; no reaction to regular insulin 6 wks. later.
F. G.	Local	12	Lilly	Special	Relieved.
P. G.	Local	10	Lilly	Mulford, Stearns Spec.	Sensitive; insulin discontinued.
J. H.	Local	10	Squibb	Special	Relieved.
H. H.	Local	9	Lilly	Lilly Spec., Hog insulin	Relieved; later able to take regular insulin.
R. L.	Local	7	Lilly	Lilly Spec., Hog	Sensitive; insulin discontinued.
P.	Local	6	Stearns	Hog, Spec.	Able to take special insulin after 1 mo.
L. R.	Local	10	Lilly	Mulford, Lilly Spec.	Relieved by Mulford.
E. S.	Local	9	Lilly	Special	Relieved.
S. S.	Local	9	Lilly	Special	Relieved.
M. S.	Local	7	Lilly	Special	Relieved; 6 wks later took regular insulin.
H. S.	Local	10	Lilly	Special	Relieved; 2 mos. later took regular insulin.
M. S.	Local	30	Lilly	Special	Relieved.
R. T.	Local	10	Lilly	Special	Relieved; 1 mo. later no reaction to regular insulin.
S. F.	Local	10	Stearns	Special	Relieved.
H. S.	Local	12	Lilly	Special	Relieved.
E. R.	Local	11	Lilly	Special	Relieved.

Some reports have recently appeared of cases of urticaria due to physical causes, which have demonstrated a remarkable therapeutic response to the use of histamin injections. Bray⁶ reported the case of a boy, aged 8, who experienced localized and generalized allergic reactions to cold water. Placing his hand in cold water at a temperature of 45° F. resulted in localized redness, swelling and itching of the immersed hand, followed by generalized symptoms of headache, faintness, dyspnea, cough and a depression in temperature and blood pressure. A successful immunity to this form of physical allergy was affected by repeated injections of histamin hydrochlorid. Mueller⁷ reported the case of a woman, aged 29, who developed periodic edema of the left hand, occurring every 14 days and lasting for 7 days, which had been treated with milk and pituitrin injections without any improvement in the condition. Repeated injections of increasing doses of histamin brought about a temporary desensitization which lasted for 5 weeks, after which the edema reappeared. Another series of histamin injections was given, and 11 months after the last injection there had been no reappearance of the swelling.

In view of the cases just reported on the favorable influence of histamin on states of physical allergy, we felt that such therapy might present some measure of potential value in the insulin-sensitive diabetic. We decided to study the effect of repeated injections of histamin on a patient who had been continuously sensitive to all types of commercial insulin for a period of 1 year.

Case Report. J. A., male, aged 58, had been diabetic for over 9 years, during the first 8 of which the condition was controlled by diet alone. In November, 1932, he had a sudden break in sugar tolerance, necessitating his return for treatment. He complained of weakness, weight loss, polyuria, polydipsia, sleeplessness, headaches, a voracious appetite and constipation. The physical examination disclosed nothing significant except evidences of wasting. The blood pressure was 146/90. He was excreting 2.5% sugar in the urine, a total of 25 gm. in 24 hours. His fasting blood sugar was 186 mg. His weight was 123 pounds; his height, 5 feet 3 inches. He was placed on a diet containing carbohydrate, 180 gm., protein, 60 gm., fat, 150 gm., having a caloric value of 2400 and containing 231 gm. of available glucose. He was given 10 units of Lilly insulin (U-40) b. i. d. At the end of a week he had gained 1½ pounds, his fasting blood sugar was 140 mg. per 100 cc. and the excretion of glucose in his urine was only a trace. Twelve days after insulin therapy was instituted he developed local reactions at the site of injection, characterized by redness, heat, swelling, induration, itching and pain. These reactions came on 6 to 8 hours after the injection and lasted about 36 hours. He was then ordered to take Lilly Special insulin (U-40) to which he reacted similarly. Intradermal skin tests were then performed with the following samples of insulin: (1) Lilly, (2) Lilly Special (prepared from beef pancreas only), (3) Lilly Hog, (4) Stearns, (5) Mulford and (6) Squibb. The local reactions were strongly positive and equal in all cases. As a result of this experience we found it necessary to stop the administration of insulin and treat him with dietetic measures. He was then placed on a diet containing carbohydrates, 125 gm., protein, 60 gm., fat, 200 gm., with a caloric value of 2500, and containing 181 gm.

of available glucose. On this diet he excreted 12 gm. of sugar in 24 hours, and his fasting blood sugar was 154 mg. On October 20, 1933, subcutaneous injections of histamin phosphate were started, beginning with 0.1 mg. and gradually increasing the dose until he was receiving 1 mg. per dose. Injections were given 3 times a week for 13 doses. For the first 10 days he continued to take insulin on those days on which he did not receive histamin. About 1 hour after taking the insulin he developed either local areas of induration at the site of injection, or generalized urticarial wheals and itching over the entire body. After the 4th injection of histamin insulin was stopped until after the 8th injection, when he received 1 mg. of histamin. The histamin was stopped, and insulin therapy instituted once more for a period of 1 week. During this time he developed local reactions at the site of injection, and although the reactions were much milder than those he formerly experienced, it was decided to stop the insulin and give him another series of histamin injections, starting with 0.5 mg. for 1 dose, and then giving 4 injections of 1 mg. each. The reactions to the histamin were characteristically uniform throughout the treatment, differing only in severity. At the site of injection he developed a local reaction which consisted of severe itching, wheal formation and surrounding erythema. There were generalized reactions of marked flushing of the face, headache, sweating of the face, paresthesias of the palms of the hands, dizziness, sneezing and depression of blood pressure.

After the last injection of histamin the patient was put on a diet containing carbohydrates, 170 gm., protein, 75 gm., fat, 140 gm., with a caloric value of 2240, and 10 units of insulin once a day. It is now 6 months since histamin was given, and he has been taking 15 units of insulin daily without any local reaction whatever.

Discussion. The rationale of the use of histamin as a therapeutic agent for desensitizing immunologically sensitive individuals is not clear to us. The rôle of histamin in immunology has been subjected to a considerable degree of investigation. Lewis and Grant,⁸ in studying vascular reactions of the skin to injury, have produced evidence to indicate that the wheal resulting from stroking of the skin contains a histamin-like substance. Their theory is that histamin is locked up in the tissue cell and is suddenly released by skin injury. Histamin will similarly be liberated in response to scratching, pricking and heat. The reports of cases of physical allergy such as the development of localized edema of an extremity following immersion in cold water seems to fall into the category of factitious urticaria resulting from skin injury and resembles the experimental phenomena of Lewis and Grant. It would appear, on the face of it, that the edema fluid in these cases contains histamin-like substances, although there has been no experimental evidence to prove this point. How, under such circumstances, the repeated injections of histamin is beneficial in cases of physical allergy or factitious urticaria is difficult for us to understand. In spite of the difficulty in interpreting the therapeutic mode of its action, we have been struck with its beneficial effect in the treatment of physical allergy and, in our case, of insulin hypersensitiveness.

There seems to be every indication that the phenomenon of insulin hypersensitivity is an antigen-antibody reaction. The supporting

evidence for this concept is (1) that local passive transfer of sensitized serum has given positive results, and (2) that it takes approximately 8 to 10 days for the sensitivity to develop, closely resembling the incubation period of serum sickness. It is difficult to conceive that the sensitization arises from the complex protein molecule itself, because up to our present degree of understanding, crystalline insulin, from whatever source, seems to have the same type of chemical construction. In view of the fact that most patients obtain relief from these reactions by changing the commercial brand of insulin, it would appear that the guilty protein is not in the insulin molecule itself, but in the protein carried along through the various stages of so-called purification. As a matter of fact, the evidence that the insulin molecule is a protein has not been absolutely established, for evidence has been presented to show that the crystalline insulin of Abel is not the molecule of insulin itself but may be a crystal of protein to which the activated insulin has been adsorbed.⁹

Summary and Conclusions. 1. The incidence of local insulin hypersensitiveness has been discussed. In our collected series of 408 insulin-treated diabetics we found an incidence of 7.3%.

2. This phenomenon appears to be an antigen-antibody reaction.

3. Favorable therapeutic results have been obtained by means of insulin desensitization.

4. Our best and quickest therapeutic effect was produced by repeated injections of histamin phosphate. A case is reported.

NOTE.—We wish to express our appreciation to Eli Lilly and Company for their cooperation and assistance in this study.

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SIGNIFICANT ACTIVE PULMONARY TUBERCULOSIS IN THE APPARENTLY HEALTHY ADULT. A STUDY OF 141 CASES.

By HAYNES HAROLD FELLOWS, M.D.

ASSISTANT MEDICAL DIRECTOR, METROPOLITAN LIFE INSURANCE COMPANY,
NEW YORK CITY.

It is imperative to detect pulmonary tuberculosis in its earliest stage both for the most successful treatment of the patient and for the control of the disease from a public health standpoint. This

is fundamental and so generally accepted that amplification of this statement is unnecessary. How to attain this ideal is the question.

The purpose of this report is to record such an attempt with the results obtained to date. Before proceeding with the actual report, a few words of explanation are necessary. Prior to 1927, applicants for employment at the Home Office of the Metropolitan Life Insurance Company received an average careful and thorough physical examination before acceptance. Those persons admitting a history of a condition associated with pulmonary tuberculosis and those who presented unusual physical signs received a Roentgen ray examination of the chest. After appointment each Home Office employee received an annual physical examination and such laboratory examinations as were necessary. In spite of these precautions, it was not unusual to detect advanced pulmonary tuberculosis in an employee shortly after a negative physical examination. There were two possibilities to consider: (1) we might be dealing with a type of disease of rapid onset and progression or (2) our method of physical examination of the lungs had shortcomings. It was decided to attempt to determine where the truth lay. Admittedly, a routine Roentgen ray film of each individual at a pre-employment examination or annual examination would be the ideal method of recording the absence or presence of an evident pulmonary lesion. The expense of such a procedure was considered prohibitive unless proved necessary. As a substitute, fluoroscopes were installed and the entire medical staff was trained to make a fluoroscopic examination of the thorax in addition to the usual physical examination. The sole purpose of such an examination was to determine whether or not we were dealing with a healthy adult chest, or whether more intensive study by Roentgen ray was indicated. Our experience with the fluoroscopic examination, gained in the past 7 years, has convinced us that it is most important and we believe that no physical examination should be considered complete without either a Roentgen ray film or a fluoroscopic examination of the thorax. So much by way of introduction.

The points of particular interest in this report are:

A. The cases studied were adults with significant active pulmonary tuberculosis.

B. The group included an encouragingly large proportion of minimal cases.

C. The majority of the cases were detected before the patients became "ill."

D. The majority of cases were detected before physical signs were evident.

E. Positive sputum or positive guinea-pig were relatively numerous at some time during the period of treatment.

A. The diagnosis of pulmonary tuberculosis was confirmed on 131 (93%) at the Metropolitan Life Insurance Company Sanatorium

at Mount McGregor. The other 10 (7%) cases did not go to the Sanatorium and the diagnosis was established in a logical, orderly fashion by the Home Office Medical Division or outside agencies.

While the large majority of the cases were detected between the ages of 17 and 24, yet it is to be noted that 27 of the cases were over 25 at the time of initial diagnosis (see Table 1).

TABLE 1.—SEX AND AGE AT DIAGNOSIS ACCORDING TO THE REASON FOR TAKING THE ROENTGENOGRAM ON WHICH DIAGNOSIS WAS MADE.

Reason for taking Roentgenogram.	Males.				Females.			
	Total.	Age 17-19	Age 20-24	Age 25 and over.	Total	Age 17-19	Age 20-24	Age 25 and over.
History	11	5	2	4	62	16	37	9
Fluoroscopic findings	10	1	6	3	49	6	34	9
Routine re-Roentgenogram	1	..	1	..	8	2	4	2
Total	22	6	9	7	119	24	75	20

B. Ninety-one (65%) were detected in the minimal stage; 42 (30%) in the moderately advanced; and 8 (5%) in the far-advanced stage. The proportion of minimal cases in this group admitted to our Sanatorium for treatment is about five times as great as the average admission rate of minimal cases reported by Hill and Williams in a survey of representative sanatoria made in 1929 (see Table 2).

TABLE 2.—STAGE AT DIAGNOSIS ACCORDING TO THE REASON FOR TAKING THE ROENTGENOGRAM ON WHICH THE DIAGNOSIS WAS MADE.

Reason for taking Roentgenogram.	Total.	Minimal.	Moderately advanced.	Far advanced.
History	73	44	23	6
Fluoroscopic findings	59	41	16	2
Routine re-Roentgenogram	9	6	3	—
Total	141	91	42	8

C. It should be emphasized that in this entire group of patients there were only a very few who were toxic or would be considered as obviously "ill" from a clinical standpoint.

There were 47 (33%) who were symptom-free, and it was only after close questioning that 13 (9%) admitted fatigue only, 18 (13%) cough, or cough and expectoration alone, and 14 (10%) slight chest pain only. In other words, 92 (65%) were symptom-free or had only one symptom, not in itself pathognomonic (see Table 3).

D. Of the entire group of 141, only 59 (42%) had râles at either

the examination at the Home Office or on admission to the Sanatorium; 6 (4%) had evidence of pleurisy with effusion.

TABLE 3.—SYMPTOMS ELICITED AT HOME OFFICE AT TIME OF ROENTGENOGRAM OR AT EXAMINATION A FEW DAYS AFTER DIAGNOSIS WAS MADE; ACCORDING TO STAGE.

Symptoms.	Total.	Min.	M. A.	F. A.
No symptoms . . .	47	37	9	1
Fatigue only . . .	13	10	3	—
Cough only . . .	18	8	6	4
Chest pain only . . .	14	10	4	—
Hemoptysis only . . .	4	2	1	1
Two or more symptoms	45	24	19	2
Total	141	91	42	8

There were 63 who had lost 3 pounds or more; 27 who had gained 3 pounds or more; and 51 whose weight has been stationary (± 2 pounds) within the year prior to establishing the diagnosis (see Table 4).

TABLE 4.—WEIGHT CHANGES WITHIN 1 YEAR PRIOR TO DIAGNOSIS; ACCORDING TO STAGE OF DISEASE.

Stage	Total.	Loss 6 pounds or more.	Loss 3-5 pounds.	Stationary + or - 2 pounds.	Gain 3-5 pounds.	Gain 6 pounds or more.
Min. . .	91	25	16	32	13	5
M. A. . .	42	10	9	17	2	4
F. A. . .	8	1	2	2	2	1
Total . .	141	36	27	51	17	10

E. Of the 131 cases who went to the Sanatorium, 25 had a positive sputum, 12 a positive guinea-pig, and 4 had a positive sputum and positive guinea pig at some time during the course of their treatment, and 90 had negative laboratory reports. Thirty-one per cent, then, had either a positive sputum or a positive guinea-pig at some time during their treatment.

TABLE 5.—LABORATORY FINDINGS BY STAGE AT TIME OF DIAGNOSIS; 131 PATIENTS WHO WENT TO THE METROPOLITAN LIFE INSURANCE COMPANY SANATORIUM.

Stage.	Cases.	Negative laboratory findings.	Sputum positive.	Guinea-pig positive.
Min. . .	83	72	8 (3)	6 (3)
M. A. . .	41	16	17 (1)	9 (1)
F. A. . .	7	2	4	1
Total . .	131	90	29 (4)	16 (4)

Cases in parentheses had positive sputum and positive guinea-pig.

Of those who went to the Sanatorium, 73 first had Roentgen ray examinations because of a slightly suggestive history; 28 (38%) of them had a positive sputum or guinea-pig test or both.

Of those 68 who had Roentgen ray examinations because of fluoroscopic findings or as a routine reëxamination 13 (19%) had positive sputum or guinea-pig test or both during treatment (see Table 5).

It is interesting to note that there were only 26 known or questionable cases of contact.

Conclusion. It is possible to detect cases of active pulmonary tuberculosis roentgenologically before symptoms and physical signs become established.

I wish to express my appreciation to Mrs. Margaret G. Stephens and Miss Margaret Wichmann for their part in the preparation of this paper.

THE TUBERCULIN REACTION IN RHEUMATIC FEVER.

BY FRANCES PASCHER, M.D.,

CLINICAL ASSISTANT IN PEDIATRICS, THE JEWISH HOSPITAL OF BROOKLYN,
BROOKLYN, N. Y.

(From the Department of Pediatrics, The Jewish Hospital of Brooklyn, Dr. Benjamin Kramer, Pediatrician-in-Chief.)

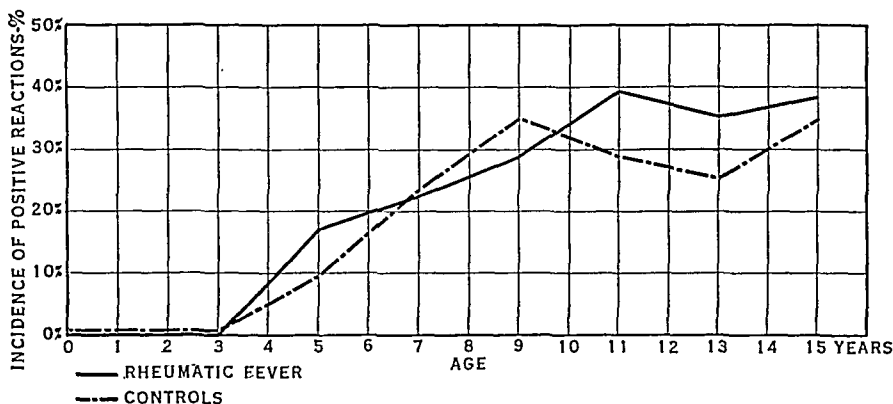
THE similarities between rheumatic fever and tuberculosis have been pointed out for many years. The two diseases have been compared clinically,^{1,15} epidemiologically,¹⁶ pathologically¹¹ and immunologically.¹¹ More recently the similarities in the skin manifestations of both diseases have been emphasized.^{17,20} New interest has been aroused in the whole subject by the work of Liebermeister,²⁰ Reitter and Löwenstein.^{21,28} The latter found as high as 70% positive cultures for tubercle bacilli in blood of patients with rheumatic fever.

With these interesting considerations as a background, we thought it would be of interest to study the nature of the tuberculin reaction in rheumatic fever. From an earlier investigation made by Sulzberger and Feit,²⁹ on a group of 20 children with rheumatic fever in the quiescent stage, and with cardiac decompensation, it appeared that patients with this form of infection were less sensitive to tuberculin than the normal. After discussion with Dr. Sulzberger we agreed that, in order to determine whether or not the reaction to tuberculin in rheumatic fever subjects was altered, a more comprehensive study was essential.

In our series we studied the reaction of 245 patients with rheumatic fever. The group consisted of children between the ages of 2 to 15 years. During the active phase of the disease 157 cases were tested, 88 during the quiescent stage and 35 tested during both periods. Inactive as well as active cases were included in order to determine whether or not the degree of tuberculin sensitivity might be influenced by the activity of the infection. The series also

included 44 cases of chorea, 16 of which were retested after the choreiform movements had completely subsided. The studies were carried out on cases of rheumatic fever admitted to the Pediatric Division of the Jewish Hospital of Brooklyn. The active series included patients with joint, nervous system, cardiac and skin manifestations, either individually or in combination. Those with cardiac disease were in the majority of instances classified as II A II B (American Heart Association classification). Only patients without symptoms or signs of activity and with a sedimentation time of over 2 hours (Linzenmeir method) were considered inactive.³⁰

The initial test was made with 0.1 mg. of Old Tuberculin (N. Y. City Board of Health) injected intradermally (Mantoux).



Incidence of positive reactions: Rheumatic subjects and controls.

When this first injection produced no reaction, the patients were retested with 1 mg. and 5 mg. (respectively 0.1 cc. of a 1 to 1000 dilution, 0.1 cc. of a 1 to 100 and 0.1 cc. of a 1 to 20 dil.). Sterile carbosaline was used as a control. Patients were observed for local, general and focal reactions.

As the control group 273 patients of comparable age were employed. The controls were selected from admissions to the service suffering from various febrile and afebrile conditions not including rheumatic fever or tuberculosis. Moribund patients, cases of sepsis or of questionable diagnosis were also excluded. It was felt that such controls would be more exact than healthy school children, since Hart³¹ and others have shown that most febrile conditions tend to lower the tuberculin reactivity to some degree. It was reasonable to assume that rheumatic fever would probably exert the same non-specific effect as other infections, and in comparison with a healthy group would, therefore, probably show a lowered incidence of tuberculin reactivity. By using hospital patients, both febrile and afebrile, as in the rheumatic group, such a source of error was obviated. The following observations were made:

1. The total incidence of positive tuberculin reactions in rheumatic fever subjects was found to be approximately the same as in the non-rheumatics.

(a) Total incidence of positives in rheumatic fever, 26.9%.

(b) Total incidence of positives in control group, 24.4%.

2. The incidence of positive reactions for each age group was approximately the same in the rheumatics and the non-rheumatics (Table 1).

TABLE 1.—POSITIVE TUBERCULIN TESTS IN RHEUMATIC FEVER.

Age group.	Rheumatic fever.		Controls.	
	Number tested.	Per cent positive.	Number tested.	Per cent positive.
2 to 3	6	0	10	0
4 to 5	24	16.6	21	9.5
6 to 7	32	22.3	56	23.4
8 to 9	52	28.8	64	34.8
10 to 11	55	39.3	43	29.1
12 to 13	61	35.2	62	25.6
14 to 15	15	38.3	17	34.3
Total and average % . . .	245	25.7	273	22.3
	Av. age = 9.41 yrs.		Av. age = 9.27 + yrs.	

3. The rise in incidence of positive reactions with increasing age in the rheumatic fever series closely paralleled that of the control group (see graph).

4. The reaction to tuberculin was the same in both phases of the disease (active and inactive).

(a) Positive incidence in active group, 26.6%.

(b) Positive incidence in the inactive group, 28.5%.

(c) In 35 cases tested during the active and inactive phases of the disease it was shown that:

Twenty-two cases negative during the active stage remained negative in the inactive stage.

Eight cases positive during the active stage remained positive in the inactive stage.

Five cases negative during the active stage were positive when retested during an inactive phase; 4 of these were retested after a period of 1 year and 1 was retested after an interval of 2 years. This alteration in the reaction in the last group can be accounted for by the well-known rise in incidence of infection with increasing age as the opportunity for contact with tuberculosis increases.

(d) Four patients who were previously negative and were retested during a recurrence of active symptoms remained negative.

5. The incidence of positive tuberculin reactions in the chorea group was 22.2%, almost identical with that of the control group. The reaction to tuberculin did not change in any of the 16 cases retested after cessation of the choreiform movements.

6. No systemic effect or focal flare up following the injection of

tuberculin, such as described by Reitter and Löwenstein was observed in any patient, even when the local response was markedly positive.

Comment. The reliability of the tuberculin test as method of determining tuberculous infection, with very few exceptions, is well enough established. The notable exceptions occur:

1. During the interval between infection with tuberculosis and the development of hypersensitivity.

2. During tuberculin therapy.

3. In conditions with negative anergy, *e. g.*, cachexia, moribund states, miliary tuberculosis, postexanthemata, especially measles.

4. In conditions with positive anergy, *i. e.*, in certain skin and other diseases, *e. g.*, sarcoids, lupus pernio, lupus miliaris faciei, some case of papulonecrotic tuberculids and erythema induratum and in osteitis tuberculosa cystica of Jüngling.^{34,35,36} (For English ref. see Jadassohn,³² and Sulzberger and Wise.³³)

Two types of anergy (positive and negative) are now recognized in view of the work of Jadassohn, Pickert and Löwenstein,³⁷ Jadassohn,³⁸ Martenstein and Noll,³⁹ and others.⁴⁰

Negative anergy can again be of two sorts:

- (a) One in which the power to react to tuberculin is diminished or lost as result of an exhausted state.

- (b) Or because there has been no opportunity for the formation of hypersensitivity (as when infection has never taken place).

Positive or specific anergy, on the other hand, occurs in certain forms of tuberculosis with a relatively benign course, notably sarcoids of skin, lungs and bone (osteitis cystica).

In these patients the altered reaction to tuberculin, *i. e.*, the diminished sensitivity, has been attributed to some degree to the presence of certain substances in the blood serum and in the tissue fluids expressed from the lesions. For these fluids, when obtained from patients with a positive anergy, and when mixed with tuberculin *in vitro* in certain proportions, are found to counteract the effects of tuberculin. These substances have been designated as anticutines by Pickert and Löwenstein.³⁷

Because of the existence of positive anergy in certain forms of disease, known to be due to the tubercle bacillus, a marked decrease of sensitivity to tuberculin when regularly encountered might speak in favor of tuberculosis. However, we found no alteration in the tuberculin reaction in our patients either in the direction of hyperergy nor anergy, and may thus state that we could demonstrate no response speaking in favor of rheumatic fever being a tuberculous disease. For it seems reasonable to assume that if rheumatic fever were a tuberculous condition, as claimed by Reitter and Löwenstein, this would have been reflected in the abnormal (hyperergic or hyperergic) response to tuberculin.

Conclusions. 1. A study made of the tuberculin reaction (quantitative Mantoux) in 245 cases of rheumatic fever in childhood shows that there is no divergence from the normal in the tuberculin reactivity in this group.

2. This fact constitutes evidence against an etiologic relationship between rheumatic fever and tuberculosis.

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SEPTICEMIA: A METHOD OF TREATMENT.

REPORT OF ONE HUNDRED CASES.

BY FRED CADHAM, M.D.,

PROFESSOR OF BACTERIOLOGY AND IMMUNOLOGY, UNIVERSITY OF
MANITOBA MEDICAL SCHOOL,
WINNIPEG, CAN.

THE diagnosis of septicemia in the cases included in this report rested on two facts: (1) That the patients presented the symptoms characteristic of the disease; and (2) that blood cultures were positive. A streptococcus or staphylococcus was recovered from the blood of each patient. When considered advisable, blood cultures were repeated and confirmed.

The cases under review cover a period of 8 years and are unselected. Of the 100 patients treated, 85 recovered, a mortality rate of 15%. Excluding the 5 cases of subacute bacterial endocarditis, all of which proved fatal, the mortality rate was 10.5%.

Procedure. Numerous strains of streptococci and staphylococci are recovered from patients with septicemia or from patients with pyemic foci resulting from infection with these bacteria. The microorganisms are cultured in serum broth and a vaccine prepared. A number of rabbits are selected and inoculated with a heavy suspension of the vaccine. Vaccine is administered to the rabbit when 6 months old and the inoculations continued twice weekly throughout the useful life of the rabbit, using numerous strains of streptococci and staphylococci. The subcutaneous and intravenous route are both employed. When one of these animals is two years of age it is considered suitable for the immediate purpose in view. I keep 25 rabbits continuously immunized.

When a positive culture is obtained from a patient showing symptoms of septicemia, a vaccine of the microorganism is prepared as rapidly as possible (generally within 24 hours), and this vaccine is inoculated into a series of the immunized rabbits. On the following day, from 6 to 10 cc. of blood are withdrawn by means of a vacuum tube from the heart of one of these rabbits, the blood is allowed to clot, the serum is removed, tested for sterility, and the patient is then inoculated subcutaneously or intramuscularly with this serum. Inoculations with the vaccine of the causative organism are continued daily with the series of rabbits already immunized and which have been selected for use in the particular case under treatment. If necessary the serum from the blood of these rabbits in rotation is administered to the patient on successive days.

The patient's blood is directly matched for a compatible donor. It is of advantage to have this procedure completed on the earliest indication that the case may prove to be one of septicemia. The suitable donor reports to the laboratory and from 60 to 100 cc. of blood are withdrawn into a large vacuum tube. The blood is allowed to clot at room temperature, and subsequently placed in the ice chest for 12 to 18 hours. The serum is removed and the patient is transfused with this serum. If considered necessary, this procedure is also carried out daily, in which case it may be advisable to have more than 1 donor. As a rule, I have administered the human serum on alternate days. The average number of

combined treatments administered to the patients was 4, the greatest number administered to any single patient, 10.

No drugs were given during the course of the treatment. On occasion, whisky was prescribed as a stimulant and then sparingly. The patient was encouraged to partake of a fairly liberal diet.

Serum treatment was instituted on the average on the 6th day following the initial symptoms; the earlier administration was on the 3d day, the most delayed on the 16th day. The first treatment with serum administered to a patient with subacute bacterial endocarditis was 6 weeks subsequent to the initial symptoms.

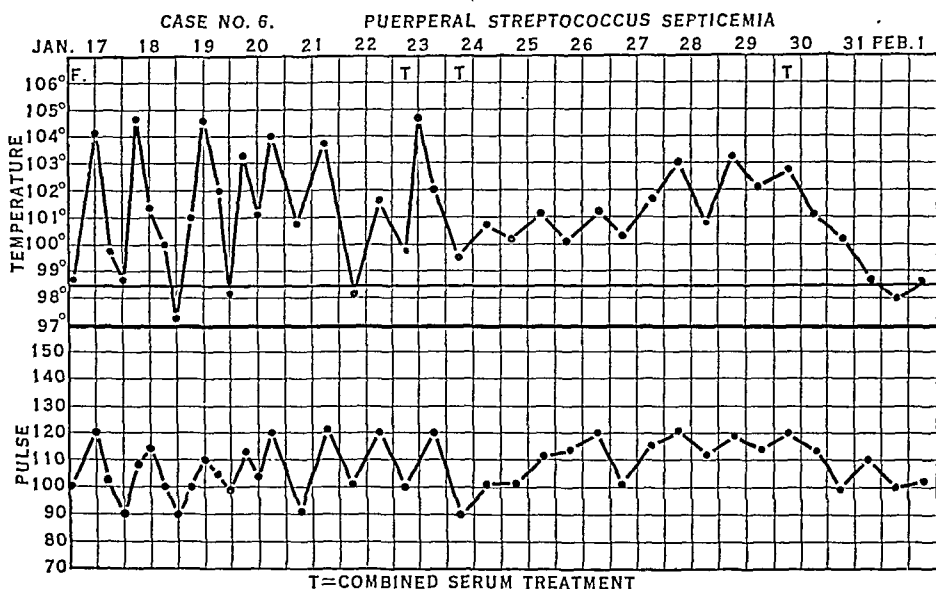


CHART I.

Clinical Notes. Frequently following the administration of the serum a definite change is noted in the character of the temperature and pulse (see charts). The patient's general condition improves and foci of infection give definite evidence of localizing. Blood cultures rapidly became sterile in the cases that recovered and remained positive in those in which there was a fatal termination, with the exception of 2 cases. One of the latter was a case of endocarditis, mentioned later, the other a young girl who had apparently recovered from the septicemia but subsequently died following the rupture into the bronchi of a lung abscess.

Of the 100 patients, 90% developed a temperature of 104° F. or over; 92% had been characterized by the sudden elevations and remissions of fever associated with septicemia. The character of the temperature range did not prove to be of prognostic value; the percentage of recoveries was as high in those patients with the greatest elevation of temperature as in those with the least. The highest temperature recorded, 108° F., occurred in a patient with

a streptococcal septicemia of puerperal origin; this unusual temperature was checked; the patient recovered.

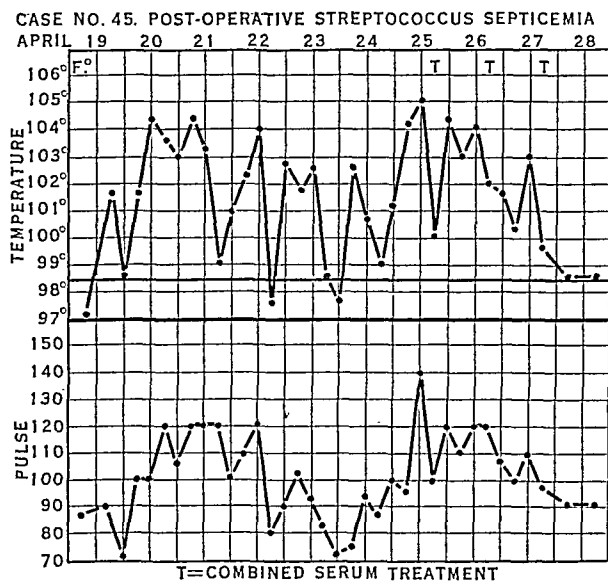


CHART II.

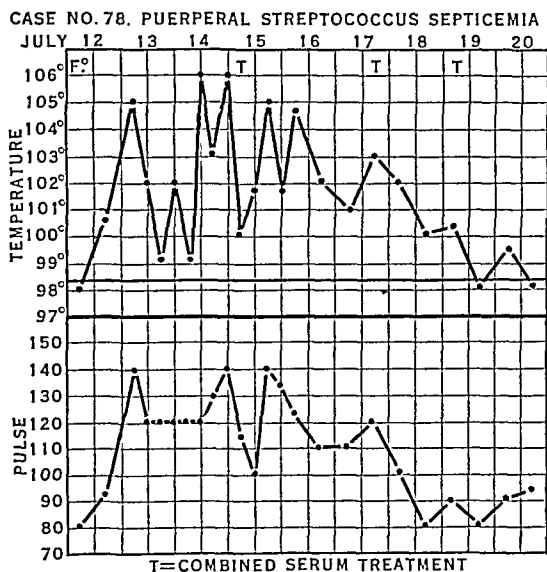


CHART III.

The pulse rate, as a rule, followed the temperature range, although in several cases it remained relatively high compared to the temperature.

Meningitis proved a serious complication in 8 patients; 6 died and 2 completely recovered. In each of these 8, symptoms of meningitis were present before serum therapy was instituted and the microorganism was recovered from the spinal fluid in 7 of them.

TABLE 1.—REPORT OF CASES (RECOVERY).

Source.	No.	Age aver.	Age range.	Sex.	Blood culture.	Complications.
Puerperal . . .	24	26	18-42	..	S. hemol., 12; strep., 12	Abscesses, 8; nephritis, 4; phlebitis, 2; total, 16.
Wounds . . .	17	30	9-60	M 12 F 5	S. hemol., 11; strep., 2; staph., 2	Cellulitis, 8; met. abscesses, 7; gangrene toes, 1.
Mastoid . . .	14	19	4-38	M 5 F 9	S. hemol., 8; strep., 5; staph., 1	Met. abscesses, 2; mastitis, nephritis, dislocated hip, bronchitis, meningitis.
Septic throat .	12	26	6-52	M 9 F 3	S. hemol., 8; strep., 3; staph., 1	Endocarditis, 3; meningitis; nephritis, 2; panophthalmitis; met. abscess.
Postop. and tooth extraction .	9	24	9-46	M 5 F 4	S. hemol., 6; strep., 2; staph., 1	Abscesses, 4; arthritis, cellulitis.
Miscellaneous .	9	15	10-44	M 9	S. hemol., 2; strep., 3; staph., 4	Osteomyelitis with met. abscesses, 4; abscesses (thigh, perinephritic, cervical), septic lung, navel infection.

S. hemol., streptococcus hemolyticus; strep., streptococcus; staph., staphylococcus; met. abscesses, metastatic abscesses.

TABLE 2.—REPORT OF CASES (FATAL).

Case No.	Age.	Sex.	Source.	Blood culture.	Complication.
39 . . .	39	F	Puerperal	S. hemol.	Staph.
10 . . .	47	F	Burn of arm	S. hemol.	B. pyocyaneus.
68 . . .	9	M	Wound of leg	Strep.	Meningitis.
70 . . .	50	M	Wound of foot	S. hemol.	Meningitis.
83 . . .	50	M	Wound of foot	S. hemol.	Pneumonia.
89 . . .	14	F	Mastoid	Strep.	Abscess lung.
88 . . .	52	F	Septic throat	Strep.	Meningitis.
44 . . .	46	M	Sinus operation	S. hemol.	Meningitis.
25 . . .	14	M	Osteomyelitis	Staph.	Meningitis.
48 . . .	35	F	Abscess of neck	S. hemol.	Meningitis.
65 . . .	45	M	Subacute bacterial endocarditis	Strep.	Staph.
79 . . .	24	F	Subacute bacterial endocarditis	S. viridans	Emboli.
80 . . .	42	F	Subacute bacterial endocarditis	S. viridans	Emboli.
81 . . .	43	F	Subacute bacterial endocarditis	S. hemol.	Pneumonia.
91 . . .	35	F	Subacute bacterial endocarditis	Strep.	Emboli.

S. hemol., streptococcus hemolyticus; s. viridans, streptococcus viridans; met. abscesses, metastatic abscesses; staph., staphylococcus.

During the later stages of the disease in 3 cases arising from a primary streptococcus infection, a secondary invader appeared in the blood stream, in 2 cases a staphylococcus and in the third the *Bacillus pyocyaneus*. In each of these patients the secondary invader, previous to its appearance in the blood stream, had been

noted in cultures made from an open lesion. Each of these 3 cases of double infection proved fatal.

No untoward effects associated with the inoculation of the animal serum were noted. On 2 occasions during the first transfusion of the human serum, although it was obtained from a supposedly compatible donor, the patient developed anaphylactic symptoms. About 3 cc. of the serum had been given when the symptoms appeared; the transfusion was discontinued; another donor was obtained for each of these patients and no reaction occurred following the administration of the second donor's serum.

A definite localizing and rapid healing of secondary foci occurred in the patients who showed improvement following the treatment and in whom metastatic abscesses had previously developed.

Comment. The experimental evidence in support of and the reason for this method of treatment I have submitted in papers previously published.^{1,2,3} As a rule, in septicemia a rapid fall in the complement power of the patient's blood occurs; transfusion of normal human serum reactivates this property. Serum is used in preference to whole-blood transfusion because the cellular elements of the donor's blood apparently lower the patient's complement.

The rabbits immunized as previously described show a high degree of resistance to experimental infection. Also, as a rule, the rabbit serum contains specific antibodies for the majority of the strains of streptococci and staphylococci recovered from the patients with septicemia. These were demonstrated by the agglutination, precipitation and bacteriolytic reactions. On occasion, however, a streptococcus is isolated from the blood stream of a patient, for which streptococcus these immune properties of the animal serum are present in but a slight degree. In such a case it is necessary to stimulate the formation of the antibodies in the rabbits by repeated inoculations with the specific organism.

In our experience withdrawal of the blood from the heart of a rabbit while anesthetized does it no harm.

The 5 cases of subacute bacterial endocarditis proved fatal. There is a question whether such cases should be classed with septicemia. The focus in the heart is the grave pathologic condition to be considered; the intermittent bacteriemia associated with this lesion is secondary. An invasion of the blood stream by a streptococcus or staphylococcus giving rise to the acute symptoms of septicemia differs from the slowly progressive bacterial invasion, so graphically described by Boyd,⁴ of a previously damaged heart. The complement power of the blood of the patients with subacute bacterial endocarditis remained constantly at extremely low levels. Following the initiation of the treatment, an apparent improvement occurred in the general condition of these latter patients. In 1 case the temperature returned to the normal level, the blood culture became sterile and the patient who had been confined to bed for

2 months was able to move about; however, the clinical evidence indicated that the heart was seriously damaged and the patient died suddenly 1 month later following slight extra physical exertion. The added injury resulting from the bacterial invasion of an already damaged endocardium, particular to subacute bacterial endocarditis, is evidently beyond the body's resources for efficient mechanical repair.

A diagnosis of the complication of acute bacterial endocarditis was made in 3 of the patients, all of whom recovered and have since remained in good health.

In septicemia prompt action is important. The early recognition of the nature of the case and the immediate application of a definite method of treatment may prove the deciding factor for a fortunate outcome.

The evaluation of the special laboratory procedures that may be undertaken in the treatment of septicemia (Kolmer⁵) presents many difficulties. Patients with the disease may, and do on occasion, recover when left to their own resources. The result in any single case depends upon the nature of the microorganism and the resistance of the host, both of which factors are variable and interdependent. The argument may be advanced that, in any series of cases such as are recorded here, the fortunate circumstance of low virulence and high resistance may play an important part in the results noted. Experimental evidence gives little aid in elucidating this problem, since septicemia in the animal varies considerably from that in man. The question of controls arises, but an accurate system of human controls is difficult to attain.

The records of the patients with septicemia from whom a positive blood culture had been obtained in our laboratory previous to the time covered by this report showed that the mortality rate was over 85%; similar statistics were obtained from a large hospital in Winnipeg. Accurate statistics on the mortality rates in septicemia resulting from a streptococcus or staphylococcus invasion originating from foci in various tissues are difficult to secure. Evidently the mortality rate in such cases is much higher than we have been content to believe.

Summary. A method is described for the treatment of septicemia by inoculation of a specific antiserum and by transfusion of normal human blood serum. A brief report of 100 cases is submitted: 85 of the patients recovered. Excluding the 5 cases of subacute bacterial endocarditis, all fatal, the mortality rate of the other 95 cases was 10.5%.

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THE VALUE OF THE CUTANEOUS HISTAMIN REACTION IN THE PROGNOSIS OF PEDAL LESIONS IN DIABETES MELLITUS.

AFTER-HISTORIES OF 89 PATIENTS FOR FIVE YEARS.

BY ISAAC STARR, JR., M.D.,

HARTZELL PROFESSOR OF RESEARCH THERAPEUTICS, UNIVERSITY OF
PENNSYLVANIA, PHILADELPHIA, PA.

(From the Hospital of the University of Pennsylvania.)

SOMEWHAT over 5 years ago an investigation was undertaken to discover whether aid in the diagnosis and prognosis of peripheral vascular disease could be secured by the reaction of the skin to histamin.^{1,2} It was known that this response could be greatly changed by experimental obstruction of the circulation,³ and it soon became evident that abnormal histamin reactions were almost invariably associated with the other manifestations of diminished circulation in the extremities. Therefore, it has been generally agreed that the skin histamin reaction affords a simple means of roughly measuring this circulation.^{1,2,4,5,6,7}

The question then presented itself whether this simple test of circulatory efficiency could be used to detect those patients who, suffering from a disease frequently accompanied by gangrene, were in especial danger of this complication. Therefore, in 1928-29, we elicited the histamin reaction on the lower extremities of 100 consecutive cases of diabetes mellitus with the intention of keeping in touch with these patients for a prolonged period.² Somewhat over 5 years has elapsed and it has been possible to secure recent information concerning 89 of them. The results secured 5 years ago may now be compared with the outcome and the prognostic value of the cutaneous histamin response determined.

The patients with marked impairment of this reaction on their feet not only have developed a high incidence of serious trouble with their feet, but also have had a higher mortality than those with normal responses. No case with a normal response to histamin developed gangrene, persistent infections, ulceration, or intermittent claudication during the subsequent 5 years. The value of the histamin reaction, in predicting the likelihood of trouble with the feet in diabetes, seems to have been clearly demonstrated.

Method. Almost half the living patients were still attending the outpatient department of this or neighboring hospitals. Those dwelling in the city were seen in the clinic or at their homes. Information about the others was obtained by sending a questionnaire to their physicians, whose coöperation made the study possible. The visiting was performed by Miss Mary Pollock, of the Social Service Department, who also supervised

the other means of securing information. A large part of the expense was borne by the Civil Works Administration.

The normal response of the skin, to a minute amount of a 1 to 1000 solution of histamin acid phosphate pricked into it, is identical with that which follows a mosquito bite. It consists of a red spot, soon succeeded by a wheal, and surrounded by a flare. It is accompanied by itching. In normal persons all these features are manifest within five minutes. The technique of eliciting this response has been described.^{1,2} When the circulation is abnormal the appearance of the wheal and flare may be delayed, or they may not appear at all, the response consisting of the spot only, or of nothing visible. For convenience of expression the normal reaction, complete within 5 minutes in both foot and knee will be spoken of as Grade I. A reaction on the foot lacking wheal or flare, or both, at the end of 5 minutes, but complete within 10 minutes, the reaction above the knee being normal, will be referred to as Grade II. A reaction on the foot failing to become complete within 10 minutes, that above the knee being normal, will be called Grade III.

TABLE 1.—CLINICAL COURSE OF 89 PATIENTS TESTED BY CUTANEOUS HISTAMIN REACTION 5 YEARS BEFORE.

Condition of circulation of feet 5 years ago.	No. of cases followed 5 years or until death.	No. who had lesions of feet when tested 5 years ago.	Died during 5-year period.	Survivors for 5 years.	No. who survived 5 years without serious trouble with feet.	Nature of trouble developing before death or within 5 yrs.; lesions present at time of original test not included; No. of patients who developed symptoms given below.			No. of patients requiring amputation.	No. of admissions to hospital wards for trouble with feet.
						Prolonged pain without other manifestations.	Chronic infections and ulcers without gangrene.	Gangrene.		
Normal histamin reactions normal	26	0	7	19	19	0	0	0	0	0
Slightly diminished histamin reactions Grade II	31	1	8	23	19	4	0	0	0	0
Markedly impaired histamin reactions Grade III	32	7	18	14	5	6	4	4	2	10

Results. In Table 1 a summary of the results has been given. The 89 patients have been grouped according to the grade of the histamin reactions obtained 5 years before. When the response on the 2 feet differed, the more abnormal has been used to classify the case. No case with normal (Grade I) reactions has had any serious trouble with the feet during the intervening period. Those with slightly diminished (Grade II) reactions have likewise had no serious trouble. Persistent pain in the feet, not typical of peripheral vascular disease, and not definitely to be assigned to any other

cause, was reported by 4 of them. This may indicate future trouble, but nothing of any gravity has supervened during the 5 years. The one exception to this statement was the case of E. A., who had a small patch of gangrene when tested 5 years ago and who died of embolism during the next few days. Therefore, it appears evident that, if the response of the skin of the feet to histamin is complete within 5 minutes, serious trouble with the feet need not be feared. If the reaction is complete within 10 minutes such trouble should not be expected.

But the situation is far different in the remaining group, those who had a highly abnormal response to histamin on their feet. Only 14 of the original 34 survived the 5-year period, only 5 of these survivors have avoided serious trouble with their feet. The following are brief reports of the more serious cases which I have been able to follow personally.

Case Abstracts. CASE 1.—J. R., a woman, aged 67, has been diabetic since 1919, and is now on insulin. In 1928, she had a Grade III histamin reaction on both feet, no pulsation in the vessels of the feet and no color changes. The superficial vessels were moderately sclerotic. She had no serious trouble with her feet until 1930. Then the right foot began to pain and she sought admission. The foot was cold and discolored about the heel. Rest and diabetic control relieved the symptoms and she was discharged. Six months later (1931) she noted an ulcer on the 5th right toe. Six weeks of care by her doctor failed to heal it. It became increasingly painful and she again sought admission. Examination showed a necrotic lesion at the right heel, another at the right 5th toe and the right great toe was swollen, tender and painful. She remained in the hospital 3 months, during which conservative measures made but little progress. She declined amputation and was sent home with the lesions unhealed. She is still living (1934).

CASE 2.—J. J., a man, aged 57, has been diabetic since 1919. No insulin until first admission. He had a Grade III reaction on both feet when tested in 1929. At this time the dorsalis pedis pulses were palpable but weak. No pulse could be felt in the posterior tibial arteries. No color changes were observed. His feet gave him no trouble until 1931, when he developed a number of ulcers which healed under treatment by his doctor. In February, 1933, the left foot became painful, then discolored, and he sought admission. Examination showed black superficial gangrenous plaques over the first metatarsal phalangeal joint, on the ball of the great toe and between 2d and 3d toes. The gangrene spread rapidly. Amputation was performed at midleg. Convalescence was uneventful. He is still living.

CASE 3.—L. B., aged 57, known to have diabetes since 1913, had Grade III reactions on both feet when admitted with an ulcer on the *right* middle toe in 1929. The left dorsalis pedis pulse was strong, the right and the posterior tibial pulses could not be felt. No abnormal color was noted on the left foot. The ulcer healed under conservative measures. She was readmitted 1 year later (1930), with a superficial gangrenous spot on the *left* great toe. Conservative measures were again successful. She was readmitted in 1932, but not because of trouble with her feet. She died after an accident later in that year.

CASE 4.—R. H., aged 50, known to have diabetes since 1925, had a Grade III histamin reaction on both feet in 1929. The pulse could be felt

in the dorsalis pedis and posterior tibial arteries. No abnormal color was observed. She had no trouble with her limbs until 1933, when after an apparently insignificant scratch the outside of the right foot became red, hot, swollen and painful and the redness rapidly extended up to the knee accompanied by burning and itching. She was admitted to the hospital and the infection subsided rapidly under hot wet dressings. Three months later she had a very similar infection, again requiring admission. This also subsided, to recur 3 times more at intervals of about 2 months, each attack requiring hospitalization. She is in the hospital at the time of writing (1934). Diagnosis, recurrent cellulitis.

CASE 5.—Another man, not in the original group of 100 cases, shows a similar outcome. C. W., aged 58, with mild diabetes, diagnosed in 1931, was tested in that year when he came to the hospital because of an ulcer in his *left* foot. The *right* foot had caused him no trouble but both feet showed Grade III histamin reactions at this time. No pulse could be palpated in the vessels of either foot. When dependent, rubor extended on to the dorsum of the left foot but was confined to the toes on the right. The lesion healed in the thermoregulated cradle.⁸ Two years later he was readmitted with ulcers on the *left* great toe and right heel. They again healed under conservative measures. In 1934, he was readmitted with a large gangrenous plaque under the *right* internal malleolus, and small ulcers on the right heel and great toe. The small ulcers healed but the gangrene spread. Amputation was performed above the knee. Thus a Grade III histamin reaction on the right foot was followed by gangrene 3 years later.

I am dependent on other physicians for reports of certain other cases in this group. A. M., with Grade III reactions on both feet in 1929, has had cramp-like pains in the legs since 1932. More recently she has had a succession of infections in the legs diagnosed recurrent phlebitis. These have not required hospitalization. E. M., who had Grade III reactions in 1929, had painful feet with chronic ulcerations before her death in 1933. A. G., with similar reactions in 1929, constantly complains of painful and swollen feet.

Discussion. In the preceding discussion histamin reactions have been classified as abnormal when either wheal or flare failed to appear. Obstruction of the circulation, whether pathologic or experimental, affects both together. In some cases, however, a good wheal is not accompanied by a flare, a condition which occurs when the peripheral nerves have degenerated.³ Before this condition is diagnosed every effort must be made to bring out the flare by allowing the part to hang down or causing venous engorgement by a blood pressure cuff inflated to 30 mm. Hg. Because of the ease of determining its presence, and because it is independent of the nerve supply, the wheal is clearly more important than the flare in estimating the peripheral circulation. Therefore, we have continued to introduce the histamin by placing a drop on the skin and pricking the skin through the drop with a sharp needle. The intracutaneous injection of histamin, preferred by some clinics,⁴ raises a wheal mechanically, and thus confuses the estimate of the histamin wheal. However, in the great majority of instances, either technique suffices.

The difference in mortality in the different groups, classified according to the histamin reaction alone (Table 1) deserves discussion. The group with markedly impaired histamin reactions has a mortality rate over twice that of the more normal groups. But the cases in this group averaged 55 years of age in 1929, those in the more normal groups averaged 44 years. In the older group more deaths are to be expected during a 5-year period. When these data are studied in the light of a standard mortality table, it is found that the difference in mortality between the groups is not greater than is to be expected at such different ages.* The histamin response gives no better indication of life expectancy in diabetes than the age of the patient.

We had hoped to obtain information concerning the relation between histamin response and the permissible level of amputation, but we have been able to secure very little data. We had anticipated² that it would be proper to amputate at a level where the histamin reaction was normal, dangerous to amputate where it was abnormal. In support of this concept may be cited 3 successful midleg amputations for diabetic gangrene when the histamin response was normal and 2 midleg amputations which failed, requiring reamputation at a higher level, when the reaction at the initial level was abnormal. But with the development of new methods, and an increasing interest in conservative procedures in recent years, we have seen a number of successful amputations of toes at levels where the histamin reaction was highly abnormal. Whether this can be accomplished without a special technique to overcome vascular spasm⁸ and increase the circulation,⁹ we do not know.

Observation of the cutaneous response to histamin and of the pulse in the superficial arteries permits the division of the cases into several groups, according to the location of the disease in small or large vessels, and the amount of vascular compensation.² It is now possible to study the outcome of the cases which, in 1929, fell into two especially interesting groups:

1. Lesions chiefly in the minute vessels (dorsalis pedis pulse strong; histamin reaction markedly impaired, Grade III). There were 8 cases in this group in 1929. Six of them did not survive the 5 years, a surprising mortality, not to be accounted for by their age, which averaged 47 in 1929. However, none of them are known to have developed serious trouble with their feet. The primary causes of death assigned by the attending physicians were heart disease (2 cases), diabetes (2 cases), nephritis and carcinoma. This heavy mortality defeated our purpose of discovering whether this condition predisposed to serious pedal lesions.

* I am indebted to Dr. L. I. Dublin for instructions as to how to compare a difference in mortality between groups of different ages on the basis of a standard mortality table.

2. Lesion in the large vessels without compensation (dorsalis pedis pulse absent, histamin reaction, Grade III). Thirteen of these cases have been followed; 8 are now dead; 6 had or developed frank gangrene. Only 1 survives without having had serious trouble with the feet during the 5-year period. The serious prognostic significance of this situation is evident.

It is of interest to compare the prognostic value of the histamin reaction with that of the most valuable single physical sign, pulsation in the dorsalis pedis artery. In Table 2 this comparison has been made on the basis of the cases surviving 5 years. In Table 3 a more exact method has been employed. The total number of years the patients in each group were exposed to risk of gangrene has been calculated. Thus, the cases surviving the 5-year period of observation were exposed for 5 years, but patients dying before 5 years had elapsed were exposed only during the period between the beginning of observation and their deaths. The ratio of the years exposed in each group to the number of patients developing serious lesions gives an index of the prognostic value. In compiling Table 3, lesions present when the tests were made, in 1929, have been disregarded, only lesions developing afterward having been included.

TABLE 2.—COMPARISON OF PROGNOSTIC VALUE OF HISTAMIN REACTION AND DORSALIS PEDIS PULSATION.

Condition 5 years ago.	No. of survivors for 5 years.	Per cent of survivors remaining free of trouble with their feet. %.
Histamin reaction normal	19	100
Dorsalis pedis pulse palpable	43	88
Histamin reaction slightly impaired (Grade II)	23	83
Dorsalis pedis pulse not felt	9	56
Histamin reaction markedly impaired (Grade III)	13	38
Histamin reaction shows no wheal in 10 minutes (flare disregarded)	11	27
Dorsalis pedis pulse absent, histamin wheal absent for 10 minutes	5	20

TABLE 3.—COMPARISON OF PROGNOSTIC VALUE OF HISTAMIN REACTION ON THE FEET AND DORSALIS PEDIS PULSATION.

Condition 5 years ago.	No. of years patients exposed to risk of trouble with feet.	No. of patients who developed ulcers, infection or gangrene.	Per cent of patients who may be expected to develop serious lesions each year.
Histamin reactions normal	106	0	0
Histamin reactions slightly impaired (Grade II)	131	0	0
Histamin reactions markedly impaired (Grade III)	106	8	7.5
Dorsalis pedis pulse palpable	295	6	2.0
Dorsalis pedis pulse not felt	48	2	4.2

Certain features of the data given in the tables have been subjected to statistical analysis.¹⁰ The striking difference between the

outcome of cases with normal and markedly impaired histamin reactions is highly significant.* But minor differences in prognostic value, as that between markedly impaired reaction and absent dorsalis pedis pulse, are not significant in so small a series of cases.

In making a prognosis the judgment should not be based on any single factor. If the information provided by the histamin reaction is supplemented by consideration of the physical findings, the age, and strength of the patient, it is to be expected that the danger of serious trouble with the feet can be foretold with considerable accuracy. Many patients can be reassured. In those threatened, extraordinary efforts to keep the feet from contact with extremes of temperature, particularly the cold of winter, to keep the skin in good condition, to avoid trauma and infection, and to treat the most trivial lesions without delay may do much to further the wellbeing and longevity of these patients.

Summary. In 1928-1929, the peripheral circulation of a series of cases of diabetes was tested by means of the reaction of the skin to histamin. The after histories of 89 of these cases have been followed for 5 years or until their death.

No case having a normal skin histamin reaction on the feet, in 1929, developed any serious trouble with the feet during the subsequent 5 years.

Of the 32 patients giving markedly impaired histamin reactions, in 1929, only 5 survived the 5 years without serious trouble with the feet. Four cases eventually developed gangrene, 4 others developed chronic ulceration or infection requiring hospitalization and 6 have suffered from painful feet without serious lesions.

The skin histamin reaction gives valuable evidence concerning the prognosis of peripheral vascular disease in diabetes mellitus. Considered together with the physical findings, this test provides a simple means of dividing cases of diabetes into a group not immediately threatened with peripheral vascular disease, an intermediate group, and a group in which extraordinary precautions must be taken to prevent the development of serious trouble with the feet.

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* i. e., The probability is less than 5 in 100 that the differences found are due to chance in the selection of the cases.

FATAL ANURIA FOLLOWING BLOOD TRANSFUSIONS. INADEQUACY OF PRESENT TESTS FOR COMPATIBILITY.

BY ELMER L. DEGOWIN, A.B., M.D.,

INSTRUCTOR IN INTERNAL MEDICINE,

AND

C. W. BALDRIDGE, B.S., M.D.,

ASSOCIATE PROFESSOR OF INTERNAL MEDICINE, STATE UNIVERSITY OF IOWA,
IOWA CITY, IOWA.

(From the Department of Internal Medicine, State University of Iowa.)

HEMOLYSIS has been the major hazard in blood transfusions since 1667, when hemoglobinuria was first reported following the transfusion of sheep blood into man,¹ until the principles of blood grouping were established by Jansky,² in 1907, and by Moss,³ in 1909. It is now generally believed that severe hemolytic reactions result only from errors in the determination of blood groups. Bordley,⁴ in 1931, reviewed 17 cases of major transfusion reactions, in all of which there was oliguria, 11 showed hemoglobinuria and 6 were jaundiced. The author stated: "In not a single case is there complete and satisfying evidence to prove that the blood of the donor was compatible with that of the recipient."

We wish to report 2 fatal transfusion reactions which occurred in November, 1933, because our findings raise a doubt as to the adequacy of the conventional methods of testing for incompatibility.

Case Reports. CASE 1.—E. A., female, aged 53, came to this hospital in October, 1931, with carcinoma of the cervix uteri and severe secondary anemia. The carcinoma was treated with radium and Roentgen irradiation. The patient, whose blood was found to be Group IV (Moss), received 2 transfusions within a week from different Group IV donors (S. G. W. and C. W. G.). There was no untoward reaction. Two examinations in 1932 and 3 in 1933 failed to reveal any evidence of neoplasm. In March, 1933, the patient noticed blood in the stools and this continued until November, when she returned to the hospital because of pallor and weakness. Again, no evidence of neoplasm could be found in the pelvis or in the gastroenteric tract. The skin over the lower abdomen was inelastic and presented many dilated venules. The mucosa of the lower bowel was thickened, inelastic and bled easily, but was not ulcerated. It was concluded that the bleeding was due to irradiation endarteritis of the lower bowel.

There was no free hydrochloric acid in the gastric secretion after histamin stimulation. Hemoglobin, 35% (Sahli); erythrocytes, 3,250,000; leukocytes, 4,600 per c.mm. There was some anisocytosis and many microcytes.

October 20, 1933: Transfusion of 400 cc. citrated blood from donor C. W. B. (Group IV, Moss) without cross-matching. The rectal temperature rose to 104.2° F. and there were headache, nausea and vomiting, but no jaundice or hemoglobinuria.

October 30: Hemoglobin, 45% (Sahli); erythrocytes, 3,550,000; leukocytes, 6000 per c.mm. After satisfactory cross-matching with the blood of donor A. L. B. the patient was given 500 cc. of citrated blood. The transfusion was followed by a slight chill, a temperature of 102.8° F. (rectal),

jaundice, albuminuria and hemoglobinuria, but no erythrocytes were found in the urine.

November 1: Capillary resistance test negative; bleeding time (Duke), 6 minutes; coagulation time (capillary tube method), capillary blood, 3 minutes, and venous blood, 5 minutes; prothrombin time (Howell), 4 minutes; hemolysis of erythrocytes began at 0.44% saline and was complete at 0.3%; the clot was normally retractile; blood platelets (Van Allen), 0.4% by volume; hematocrit (Van Allen), 32%; hemoglobin (Newcomer), 8 gm.

TABLE 1.—BLOOD CHEMICAL STUDIES AND URINARY OUTPUT IN CASE 1.

Date, 1933.	Urine.	Van den Bergh (Gibson ¹⁶).	Blood urea N, mg. per 100 cc.	Blood uric acid, mg. per 100 cc.	Blood creatinin, gm. per 100 cc.	Blood CO ₂ combining power, vol. %.	Blood chlorid, mg. per 100 cc.
Oct. 30 . .				Transfusion			
Nov. 1	4.4 indirect		Transfusion			
12 . .				Transfusion			
13 . .	50	17.4 direct					
14 . .	400	0.9 direct	79.4	6.6	4.0	35.0	
15 . .	600	0.9 direct	86.8	6.6	7.7	34.1	536
16 . .	35						
17 . .	75	...	81.9	6.8	10.0		
18 . .	85						
19 . .	50	...	94.5	...	12.0	26.8	555
			Cystoscopic examination				
20 . .	335	...	100.0	10.0	11.5		
21 . .	*	...	102.0	9.6	12.0	24.0	555
22 . .				Died			

* Incontinent.

November 12: Hemoglobin, 70% (Sahli); erythrocytes, 4,650,000 per c.mm. The washed corpuscles from 500 cc. of citrated blood of donor L. M. F. were given intravenously after compatibility had been established by grouping and cross-matching. Immediately after the transfusion the patient complained of cramps in the right thigh and lumbosacral region, and could not move her leg. There was pain in the abdomen, vomiting, chilliness and the rectal temperature reached 103.2° F. Jaundice became apparent 7 hours after the transfusion. The degree of oliguria can be seen in Table 1. All urine specimens contained hemoglobin and granular casts, but erythrocytes were not observed. Intravenous injections of saline and glucose were given and heat was applied to the kidney regions. Slight generalized edema soon became apparent. On November 17, the tests of November 1 were repeated, with essentially the same results except that hemolysis of erythrocytes began at 0.48% saline. On November 18, cystoscopic examination revealed bloody urine coming from both ureters. The kidney pelves were irrigated with very warm water. Pulmonary edema developed on November 20 and oxygen was administered. Blood (200 cc.) was withdrawn and replaced by saline.⁷ The blood of the last donor (L. M. F.) was again cross-matched with that of the patient and no agglutination occurred in 4 hours at room temperature. At the end of 18 hours there was still no agglutination, but some of the donor's corpuscles had disappeared, whereas the recipient's corpuscles were intact. Intracutane-

ous tests on the recipient with the donor's corpuscles and serum were negative. On November 22 (10 days after the last transfusion), the patient died. Permission for necropsy could not be obtained. The urinary volume and blood chemical findings are included in Table 1.

CASE 2.—W. B., male, aged 65, was admitted to this hospital, November 8, 1933, because of hemorrhage from a peptic ulcer. He was weak and pale. Hemoglobin, 27% (Sahli); erythrocytes, 1,950,000; leukocytes, 5950 per c.mm. He received the usual treatment, and by November 14 hemoglobin was 35% (Sahli). His blood was found to be Type IV (Moss) and he received a transfusion of 500 cc. citrated blood from G. D. M. without reaction on November 16. Preliminary cross-matching was satisfactory.

On November 25, his blood matched that of J. F. S., another Type IV donor, and he was given 500 cc. of citrated blood from this donor. When about 75 cc. of blood had been given, the patient complained of a cramp in the right hip which was relieved by change in position. The transfusion was resumed and the entire operation was concluded in 75 minutes. About 1 hour later he was nauseated and vomited. The rectal temperature rose to 100.4° F. and he had a slight chill. He passed no urine from the time of transfusion until his death. Fluids were given by vein, subcutaneously and by mouth. The blood corpuscles and serum of J. F. S. and the recipient were again cross-matched and no agglutination was detected microscopically.

TABLE 2.—BLOOD CHEMICAL STUDIES IN CASE 2.

Date, 1933.	Blood urea N, mg. per 100 cc.	Blood uric acid, mg. per 100 cc.	Blood creatinin, mg. per 100 cc.	Blood CO ₂ combining power, vol. %.	Blood chlorid, mg. per 100 cc.	Van den Bergh (Gibson) ¹⁶ .
Nov. 10 . .	14.0	3.1	1.0	58.7	602	0.2 indirect
16 . .			Transfusion			
25 . .			Transfusion			
27 . .	62.3	5.5	6.4	58.9	600	
28 . .	80.5	6.5	8.3	56.0	595	
29 . .	88.9	8.5	10.7			
Dec. 1 . .	125.0	10.0	13.0	45.7	585	
2 . .	141.4	10.0	15.5	35.2		
4 . .	164.0	10.0	14.0	31.5		
5 . .	183.4	10.0	17.6	Died		

On November 29, cystoscopic examination was performed and the renal pelves were washed with very warm water. This did not stimulate the urinary flow appreciably. The patient was drowsy and his muscles twitched occasionally. On December 3, he developed hiccoughs which were relieved by the inhalation of carbon dioxide. On December 5 (10th day after transfusion) he became stuporous and died. At no time was jaundice observed.

The blood chemical studies are included in Table 2.

Necropsy was performed by Dr. C. H. Coughlan. The pertinent findings, submitted by Dr. H. P. Smith, are as follows:

"The liver weighs 1950 gm. No abnormalities are made out in gross. Microscopically, one sees tiny areas of injury at the centers of many of the lobules. In such spots the liver cells are gone and there is hemorrhage, together with a few leukocytes and a few pigment-laden phagocytes. No pigment is seen elsewhere in the liver. There are a few lymphocytes in the portal spaces.

"The two kidneys are similar. Each weighs 250 gm. The capsule strips readily, leaving a smooth surface. No hemorrhages are seen. The cortex appears hyperemic and is about 7 mm. thick. The striations of the

pyramids are unusually distinct. Fine golden-yellow, longitudinal lines are noted in the lower halves of the pyramids. The pellicular surface is smooth and pink. Microscopically there are a few old areas of scarring. Elsewhere the glomeruli appear normal. They appear to be entirely free of capillary thrombi. There is widespread injury to the tubules. Some of the convoluted tubules show necrosis of the epithelium. Many of the tubules are lined by low cuboidal epithelium having bluish cytoplasm, like that seen in the late stages of mercuric chlorid poisoning. Throughout the cortex there is extensive edema of the stroma, and as a result the tubules are forced apart. In the lumina of the collecting and convoluted tubules one sees great amounts of reddish-brown granular pigment. A few of the epithelial cells in the cortex contain granules similar in appearance (Figs. 1 and 2).

"Diagnosis: Gastric ulcer. Acute tubular nephritis. Chronic cholecystitis with cholelithiasis. Hyperplasia of the prostate. Generalized arteriosclerosis."

Donors. It is well recognized in practice that some donors give more reactions than others. In our cases, 7 donors were concerned; all were members of the hospital staff and all belonged to Moss's Group IV. They had all given other transfusions. S. G. W., intern, had given about 40 transfusions without hemolytic reactions; C. W. G., intern, had given at least 35 transfusions with no major reactions; C. W. B., associate professor, had given at least 75 transfusions without any major reactions; A. L. B., nurse, had given 1 other transfusion; L. M. F., intern, 7; G. D. M., intern, 6; and J. F. S., intern, 8 transfusions, all without reactions.

Technique. The routine method of transfusion was followed in both cases, except in the last transfusion in Case 1, in which washed corpuscles were given. The blood was diluted with 100 cc. of 2% sodium citrate and a small amount of isotonic saline and administered intravenously by gravity. The solutions were made up and sterilized in the "intravenous laboratory" which supplies materials for use throughout the hospital. In November, 9 other transfusions and, in December, 14 other transfusions were given on the Medical Service with similar solutions and the same personnel. One such transfusion was followed by transient jaundice and the patient died 1½ months later of carcinomatosis. Otherwise, there were no reactions of a serious nature.

Cross-matching was done by microscopic examination of hanging drops of undiluted serum and saline suspension of corpuscles. Both the sera and corpuscles of the donors and the recipient were matched separately.

Comment. Moss stated, in 1910:⁵ "Isoagglutination may occur independently of isohemolysis but isohemolysis is probably always preceded or accompanied by isoagglutination." With this statement the majority of workers are in accord,⁶ and it is because of this opinion that the routine tests for compatibility have been reduced to agglutination tests in most clinics. However, Moss,⁵ himself, observed 3 people whose sera contained hemolysins without agglutinins. In 1919, Kolmer⁶ cautioned against the exclusive use of agglutination tests as criteria of compatibility because he had found hemolysins unaccompanied by agglutinins in human sera. Bernheim⁹ reported a case of hemolytic reaction without agglutination.



FIG. 1.—Case 2. Photomicrograph (low power) of kidney, showing collecting tubules containing brown pigment, desquamated epithelium and coagulated albumin.

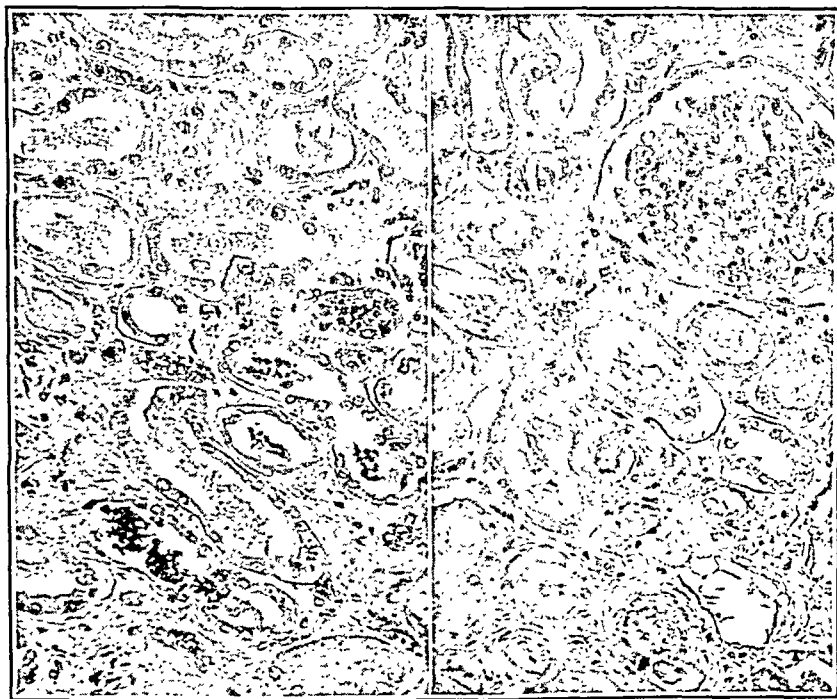


FIG. 2.—Case 2. Photomicrographs (high power), showing necrosis of tubular epithelium and lumina filled with brown pigment, desquamated cells and coagulated albumin. The stroma is edematous. A normal glomerulus is also shown.

Hesse and Filatov¹⁰ reported the case of A. Bodanov, Director of the Institute for Blood Transfusions in Moscow, who died after receiving blood apparently compatible by cross-matching. He had received many previous transfusions without reactions.

Johnson and Conway¹¹ have recently reported 3 cases of renal insufficiency after transfusions. In 1 the blood was found to be incompatible but in the others there was no sign of agglutination. Incidentally, 1 of these cases had received 4 previous transfusions.

It is obvious that the detection of hemolysis by the hanging drop method is both difficult and uncertain. There is no proof that the sera of the 4 cases cited above or that of our 2 patients would have caused gross hemolysis of the donors' corpuscles *in vitro*. We regret that tests for hemolysis by a test tube method were not done in our cases. At least 4 of the cases mentioned, in which severe reactions occurred without agglutination, had had repeated transfusions. It is possible that these patients developed hemolysins, since in our Case 1 the reactions became progressively more severe with each succeeding transfusion. Certainly if further transfusions are necessary in a patient who has previously suffered a transfusion reaction, tests for hemolysis as well as for agglutination should be done. The influence of repeated transfusions in the production of hemolytic reactions should be investigated further.

The mechanism of the production of the anuria is obscure. Yorke and Nauss,¹² and Baker and Dodds¹³ have demonstrated that the excretion of hemoglobin by the kidneys under the proper conditions will produce renal insufficiency in rabbits and that the histologic appearance of the kidneys is similar to the renal lesions in man. Newman and Whipple¹⁴ have shown that hemoglobinuria in dogs causes deposition of hemosiderin in the convoluted tubules of the kidney, as well as in the liver, spleen and lymph nodes and that a minimum renal threshold for hemoglobin is obtained when the tubules have taken up a maximum amount of the iron-containing pigment. Mason and Mann¹⁵ have shown that intravenous injection of hemoglobin has a specific vasoconstrictor effect on the kidney. Hesse and Filatov¹⁰ have recently confirmed this and have shown that the vasoconstriction can be relieved by the transfusion of compatible blood.

The fact that hemoglobin free in the blood plasma is a potent renal toxin seems established. It is as yet not possible to say whether the vasoconstrictor effect or the blocking and destruction of tubular epithelium is the more important.

Bordley⁴ has mentioned other possible explanations for transfusion anuria. Any possible toxic effect of the transfused plasma has been ruled out by the fact that our Case 1 received only washed corpuscles. The blood chemical studies in our cases effectively dispose of the theory that loss of blood chlorids or acidosis might be responsible for the anuria.

Obviously further investigations into the pathogenesis of these

unfortunate reactions are necessary before adequate means for their prevention and treatment can be determined.

Summary. Two cases are reported in which death was due to renal insufficiency definitely attributable to transfusions. In neither case could evidence of isoagglutination be found. In 1 case there was questionable evidence of hemolysis. Both patients had received previous transfusions.

Conclusions. 1. The conventional method of testing bloods for compatibility by cross-matching for agglutination only is not sufficient to prevent fatal transfusion reactions.

2. Anuria in the 2 reported cases was not due to loss of blood chlorids or to acidosis.

3. The etiology of the renal damage which results in anuria following transfusions is not yet established.

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THE INFLUENCE OF GLYCIN ON CREATINURIA IN PERIPHERAL NEURITIS.

By M. J. C. ALLINSON, B.S.,

GRADUATE STUDENT, DEPARTMENT OF PHYSIOLOGY,

H. H. HENSTELL, M.D.,

AND

H. E. HIMWICH, M.D.,

ASSOCIATE PROFESSOR OF PHYSIOLOGY, YALE UNIVERSITY SCHOOL OF MEDICINE,
NEW HAVEN, CONN.

(From the Laboratory of Physiology, Yale University School of Medicine.)

THE striking changes in creatin metabolism observed in the primary muscular diseases have stimulated new interest in this subject. In 1921, Gibson and Martin¹² found that ingestion of

gelatin increased the creatinuria in progressive muscular dystrophy. Brand and Harris,^{8,9,10} demonstrated that glycine was the fraction of gelatin responsible for this change. Milhorat, Techner and Thomas,^{18,19,22} and Kostakow and Slauck^{14,15} confirmed Brand's observations and also showed that under the influence of glycine the initial increase in creatinuria was followed by a fall in creatinine excretion with a concomitant rise in urinary creatinine. With these changes the patients manifested an increased ability to retain exogenous creatine. Beard and Tripoli,^{1,2} Mettel and Slocum,¹⁷ and Reinhold *et al.*²⁰ are among the most recent to report increases in creatinine output after glycine feeding.

In myasthenia gravis qualitatively similar changes in creatinine excretion have been obtained on feeding glycine by Boothby and his coworkers,^{5,6,7} and Remen.²¹ Reinhold and coworkers²⁰ found glycine raised the creatinuria in a case of chronic myositis resembling progressive muscular dystrophy. Harris and Brand¹³ also found moderate increases in creatinuria when glycine was fed in Charcot Marie tooth disease and periodic familial paralysis.

The creatinuria existing in the clinical conditions in which secondary atrophies occur responds very slightly or not at all to glycine. The creatinine output is not affected in amyotrophic lateral sclerosis, "muscular atrophy" and hemiatrophy, according to Harris and Brand.¹³ No changes were noted by Milhorat¹⁹ in amyotrophic lateral sclerosis, severe chronic rheumatism, congenital idiocy, deforming arthritis, spastic paralysis and progressive spinal atrophy. Kostakow and Slauck^{14,15} observed no reaction in "secondary atrophies." In contrast with these findings, Beard and Tripoli^{1,2} reported a marked increase in creatinine excretion, resulting from the administration of glycine in spinal muscular atrophy. Harris and Brand¹³ also found a moderate rise in creatinuria in a postencephalitic. The data thus indicate that with these two exceptions, the ingestion of glycine usually has no effect in secondary muscular atrophy. It might, therefore, be expected that glycine would not influence the creatinuria in peripheral neuritis with muscular atrophy. The only instance of plumbism treated in this way is Case 7a, studied by Harris and Brand.¹³ Daily administration of 10 gm. of glycine for 1 week produced no effect on the creatinuria of this woman. The present case of toxic peripheral neuritis was studied to determine the response to glycine.

Case History.* J. P., Polish, male, aged 53, was admitted to the New Haven Hospital on July 3, 1933, complaining of progressive weakness and pain of the extremities and inability to walk. On May 4 he began to feel sick, feverish and vomited. The next day he was unable to get out of bed and the day after that he felt a soreness in his fingers and feet. The vomiting persisted for 4 days. On May 11, examination by his phys-

* We wish to express our thanks to Dr. L. Greenburg, of the Department of Public Health, who first brought the patient to our attention.

ician revealed severe cough, fever, moist râles at both bases of the lungs and marked ataxia of the legs. His abdominal and deep reflexes were normal and there was no tenderness over the nerve trunks. The respiratory symptoms subsided in about 2 weeks, but the ataxia became more severe and pains developed in his hands and feet. Neurologic examination at the Grace Hospital revealed moderate atrophy of the extremities, paresthesias of the finger tips and legs and absence of kinesthetic, stereognostic and vibratory senses in fingers and toes. The tendon reflexes were now markedly diminished and the abdominal reflexes almost absent.

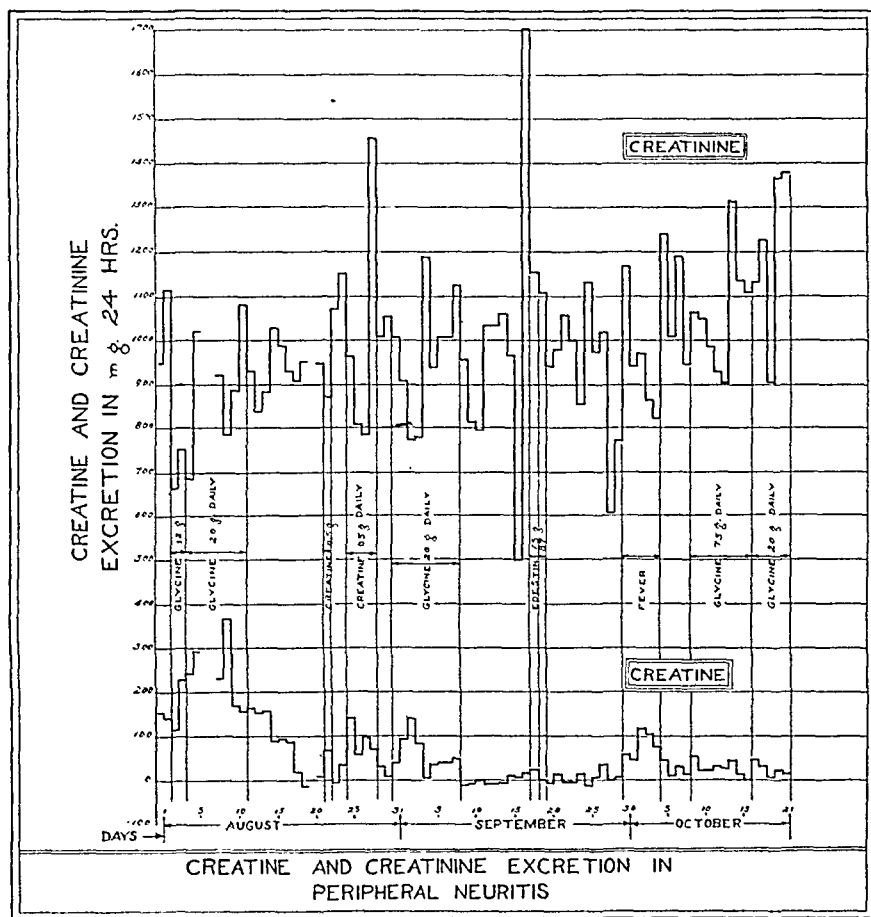


CHART I.

Urinary retention and pyuria were also present. He received mercury succinimid (gr. $\frac{1}{6}$ q.d. for 6 days) and was discharged against advice, unbenefited. He was again seen by his physician about 3 weeks after discharge, at which time ataxia and weakness had so progressed that he was unable to walk or feed himself. He was then referred to the New Haven Hospital for further care. Examination on July 3 revealed an undernourished male with marked atrophy and flabbiness of the extremities. The extensors were more involved than the flexors. Coarse fibrillary twitchings were seen in the arms and legs. The deep tendon reflexes could not be elicited. Weakness and ataxia of all extremities were marked. Sensory examination

revealed a gauntlet and stocking impairment of all superficial sensations, including vibratory sensibility. Deep muscle tenderness was increased. The blood count was: R.B.C., 4,700,000; hemoglobin, 92%; W.B.C., 9800 (polym., 98%; L.M., 7; lymphocytes, 38; eosinophils, 7). The teeth were worn and carious. The cardiorespiratory, gastro-intestinal and genito-urinary systems were essentially negative.

With a tentative diagnosis of peripheral neuritis, search for a possible cause was made. His occupation had been that of mixing and forking fertilizer containing calcium cyanimid, in an almost completely enclosed bin for 3 months previous to his present illness. He had also drunk alcoholic beverages in moderate quantities for a number of years, although for some months previous to his admission his intake had been limited by his financial situation. No other possible contributory agents were noted.

The patient was placed on a liberal diet supplemented with liver, iron and yeast. Shortly before the experiments were begun, all creatin extractions were omitted from the diet which now contained protein to the extent of 90 gm. and had a caloric value of 3000 calories. It was to this basal diet that glycine or other amino acids were added at various times. Physical therapy consisted of Osgood splints on the feet, a heated cradle over his lower extremities, massage and tank bathing.

His course at the hospital was marked clinically by a fairly rapid return of all forms of sensation except vibratory sense, in the upper extremities and then to the lower. The reflexes were slow in reappearing. At the time of discharge motor and sensory power were practically restored in the upper and somewhat less completely in the lower extremities. Diminished sensation persisted in the distal portions of the toes and soles. The triceps reflex had returned and was accompanied by a more definite periosteal radial reflex. The patient was able to walk on crutches or behind his wheelchair when he was discharged improved on October 30.

Experimental Data. Glycine, edestin, glutamic acid and creatin were separately added to the basal diet at intervals and equivalent amounts of protein were removed when edestin was fed. Analyses of total urinary nitrogen (Kjeldahl), sulphur (Benedict³), creatinin and creatin (Folin and Benedict⁴) were carried out daily. The Folin-Benedict method may occasionally give small negative values in the absence of creatin. The changes in creatin excretion are charted.

Results and Discussion. Glycine was given at 3 different periods. The first feeding of 20 gm. glycine daily for 11 days caused a prompt but temporary rise in creatin excretion from 0.118 to 0.368 gm. per 24 hours, and then a fall to 0.161 gm. per 24 hours.

When glycine was discontinued the creatinuria gradually diminished to 0. Glycine was fed again a month later for 10 days, this time eliciting a briefer rise in creatin output, from 0.01 to 0.138 gm. per 24 hours and returning to 0.048 gm. per 24 hours. After omitting glycine from the diet it was found that all but a trace of creatin disappeared from the urine. The third time glycine was given (7.5 gm. for 8 days; 20 gm. for 5 days) there was only a slight rise in the creatin excretion, but there was always some creatin in the urine as long as glycine was fed. The patient experienced mitigation of pain and stiffness shortly after the beginning of administration of glycine. During the long interval (August 12 to September

30) between the first and second periods of glycine ingestion, the stiffness in his legs and arms became progressively worse. The neurologic observations made at intervals of 3 weeks indicate progressive but slow recovery, although this improvement cannot be correlated definitely with the short period of glycine feeding. However, as the clinical condition improved, there was a gradual diminution in the extra creatinine excreted in response to glycine.

Other amino acids did not yield the same results. No changes in creatinine output were observed with edestin (rich in glutamic acid and arginine) and glutamic acid. The feeding of creatinine in 0.5-gm. doses resulted in excretion of about 20% of the ingested amount. The elimination of so small a portion of the exogenous creatinine may be attributed in part to the earlier ingestion of glycine. Paresthesias were noted during the creatinine administration, resembling the observations of Chanutin¹¹ in progressive muscular dystrophy.

The other urinary constituents did not present the cycle of changes observed with creatinine. The inconstant creatinine excretion which will not be described in detail, is similar to that found by Gibson and Martin,¹² and Magee¹⁶ in progressive muscular dystrophy. The deviations in nitrogen and sulphur excretion were not great, these substances tending on the whole to lessen throughout the period of observation.

The appearance of an intercurrent fever during the course of the experiment was accompanied by an increased creatinine output. Of particular interest is the fact that the increased creatinuria preceded the elevation of the temperature and persisted a short time after its return to normal.

Summary. A case of toxic peripheral neuritis with atrophy and creatinuria was studied. Daily analyses were made of urinary excretion of creatinine, creatinine, nitrogen and sulphur. In contrast with other cases of secondary muscular atrophy, but like those with progressive muscular dystrophy and myasthenia gravis, the ingestion of glycine markedly increased the creatinuria. The absence of response to edestin or glutamic acid was also noted.

As the patient's condition improved, the creatinuria decreased and the reaction of glycine correspondingly diminished.

We are grateful to the Staff of the Medical Service of the New Haven Hospital for assisting us wholeheartedly in this study.

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THE EXOPHTHALMOS OF GRAVES' DISEASE. ITS EXPERIMENTAL PRODUCTION AND SIGNIFICANCE.*†

BY DAVID MARINE,

DIRECTOR OF LABORATORY DIVISION,

AND

S. H. ROSEN,

ASSOCIATE LABORATORY DIVISION, MONTEFIORE HOSPITAL,
NEW YORK.

(From the Laboratory Division, Montefiore Hospital.)

THE chronic bilateral exophthalmos that develops in the course of Graves' disease in about one-third of the cases has attracted the attention of anatomists, neurologists, ophthalmologists, physiologists and pathologists alike and each has contributed to its elucidation as well as to the confusion which at present attends it. The recent independent development of two methods of readily producing exophthalmos experimentally in susceptible animals, namely, (a) by the injection of anterior pituitary emulsions or extracts in young ducks (Schockaert¹) and in young guinea pigs (Loeb and Friedman²), and (b) by the intramuscular injection of cyanids (preferably methyl cyanid) in young rabbits maintained on a diet of alfalfa hay and oats (fresh green prevents or abolishes the exophthalmos) (Marine *et al.*^{3,4}) has made it possible further to advance our knowledge of the cause and mechanism of this form of exophthalmos.

Many of the older theories to explain the exophthalmos of Graves' disease—namely that it was due to the accumulation of fat in the

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orbit, or edema and venous congestion, or asthenia and fatty degeneration of the somatic muscles, or myositis—are not now believed to be of primary importance, although they are important secondary and contributing or complicating factors.

We take it as established that the primary or essential cause of the widening of the palpebral fissure, the protrusion of the eyeball and the dilatation of the pupil in the rabbit, rat and guinea pig is an increased tonus of the orbital muscles of Mueller (1858)⁵ (*M. orbitalis*, *M. tarsalis sup.*, *M. tarsalis inf.*) and the pupillodilator muscle. The *M. orbitalis* in man and in monkeys is vestigial and on this account it is difficult to explain protrusion of the eyeball in these species by its contraction. Unquestionably in human Graves' disease there is usually some weakness of the somatic muscles. These orbital muscles are composed of non-striated fibers and are innervated by the sympathetic nervous system. Electrical stimulation of the peripheral end of the cut cervical sympathetic trunk in the cat, dog and rabbit (Wagner, 1859⁷) causes widening of the palpebral fissure, protrusion of the eyeball and dilatation of the pupil on that side, provided the superior cervical ganglion is intact. Injections of adrenalin also cause retraction of the lids, protrusion of the eyeball and dilatation of pupils. Unfortunately very little has been added to our knowledge of the anatomical relations and physiology of these muscles since Mueller's work. Because of this we have undertaken such a study in the rabbit where, as first shown by Mueller, these muscles are unusually well developed. In general, however, it may be stated that one group of these muscles extends from about the level of the equator of the eyeball into the upper and lower eyelids (Mueller's tarsal muscles) while the other smooth muscle mass forms a cone-shaped cylinder enclosing most of the orbital contents and extends from the margin of the bony orbit backward toward the optic foramen (MacCallum and Cornell²¹).

The nervous pathway of the sympathetic innervation of the smooth muscles of the eye, as shown by Claude Bernard⁸ and many others, is usually represented schematically by ganglion cells in the lateral horn of the spinal cord whose axones emerge at the level of the first and second thoracic segment and end around the ganglion cells in the superior cervical ganglion from which the postganglionic axones extend to the muscle.

In 1909 Karplus and Kreidl⁹ showed that stimulation of the hypothalamus in cats lateral and slightly posterior to the infundibulum caused maximum dilatation of the pupil, widening of the palpebral fissure and retraction of the nictitating membrane, thus proving for the first time a true hypothalamic center of the sympathetic. The nervous pathway from the hypothalamus to the lateral horns of the spinal cord is not known.

Our interest in exophthalmos was renewed in the fall of 1931,³ when, following the daily intramuscular injection of 0.05 to 0.1 cc.

of methyl cyanid into prepuberal rabbits maintained on a diet of alfalfa hay and oats, there was a progressive development of bilateral exophthalmos beginning in some cases as early as the 3d week after starting the injections, while in others it began as late as the



FIG. 1.—Frontal view. Rabbit 1-1339, male, at the age of 117 days and after receiving daily injections of acetonitril in doses of 0.05 to 0.1 cc.



FIG. 2.—Lateral view, same rabbit.

3d month (Figs. 1 and 2). It was much more easily produced in males than in females, and some rabbits of both sexes, but more commonly females, failed entirely to develop exophthalmos in this time period. Adult rabbits of both sexes are quite resistant. Of the two breeds of rabbits we have used, the Dutch strain is much more susceptible than our common gray strain. Along with the development of the exophthalmos there were often signs of precocious sexual development, particularly after thyroidectomy.

The most important association, however, of the exophthalmos was with goiter. Only those rabbits developed exophthalmos which also developed thyroid hyperplasia, showing clearly that there was a close relation between the degree of thyroid insufficiency as indicated by the goiter and the development of exophthalmos. With this fact established, we tried the effect of methyl cyanid on rabbits after thyroidectomy,¹⁰ and found that the exophthalmos was more easily produced and more marked in such animals than in animals with the thyroid intact. (The probable explanation of this will appear later.) This finding indicated that the thyroid hormone had nothing to do with the cause of the exophthalmos. Schockaert and later Loeb and his coworkers had shown that pituitary extracts also caused exophthalmos in young ducks and young guinea pigs respectively. Our experience with cyanid exophthalmos after thyroidectomy led us to suspect that the thyroid likewise had nothing to do with the exophthalmos produced by pituitary extracts. We, therefore, removed the thyroid gland from a number of guinea pigs and injected a potent preparation (Loeb) of the thyrotropic factor. As marked (and usually earlier) exophthalmos was obtained in the thyroidectomized guinea pigs as in the control pigs with intact thyroids.¹¹ It now appeared obvious that the exophthalmos was brought about by the stimulating action of the thyrotropic factor of the anterior pituitary and that the thyroid gland took no positive part in its causation.

As to the mechanism of the production of exophthalmos by cyanid and diet it is our opinion that cyanid anoxemia aids in bringing about a deficiency of some hormone which stimulates some hypothalamic center which in turn stimulates the anterior pituitary to excrete an increased amount of thyrotropic factor which directly through the blood stream stimulates the thyroid cells and also independently of the thyroid stimulates the higher sympathetic center in the hypothalamus controlling exophthalmos. This stimulation of the sympathetic center apparently becomes effective only when the thyroxin content of the thyroid is becoming exhausted. The fact that removal of the superior cervical sympathetic ganglion abolishes exophthalmos caused by methyl cyanid or by the thyrotropic factor, whereas it makes the smooth muscles of the eye more sensitive to adrenalin is further proof that the thyrotropic hormone causes the exophthalmos by acting through a nervous mechanism.

Methyl cyanid also causes an increased output of adrenalin but this is not sufficient to cause exophthalmos in animals with the cervical sympathetic cut or even with the superior cervical ganglion removed.

With this explanation of the mechanism of exophthalmos we can understand why large parenchymatous goiters alone or thyroidectomy alone (Gley¹²) sometimes causes exophthalmos in young rabbits (we have also observed this phenomenon) and why thyroidectomy plus cyanid nearly always hastens the onset of and increases the degree of exophthalmos in immature rabbits. Thyroidectomy, as first shown by Rogowitsch¹³ and confirmed by most subsequent observers, is the most potent physiologic stimulus to the anterior pituitary as indicated by the degree of enlargement of the anterior pituitary. Thyroidectomy stimulates the anterior pituitary to excrete more thyrotropic hormone because of the depression of oxidation processes, and if this metabolism depressant is combined with another powerful depressant of oxidation processes (cyanid) we get the earlier onset of and the more severe types of exophthalmos.

Finally there are some practical considerations that are of interest and importance. It has been known since partial thyroidectomy was first introduced into the therapy of Graves' disease that cases of Graves' disease occasionally develop exophthalmos after partial thyroidectomy, and second that exophthalmos existing at the time of operation often was made worse by thyroidectomy^{14,15,16}. The more recent subtotal thyroidectomies have undoubtedly further increased the incidence of postoperative exophthalmos. On the basis of our experimental work this could be explained by the increased thyroid insufficiency caused by the subtotal thyroidectomy which in turn calls forth a greater pituitary response.

The only medical treatment that has been found of benefit is the administration of iodine and desiccated thyroid. This, however, has not been very successful, as is indicated by the literature reports. Our attempts to cure the experimental exophthalmos of rabbits with iodine and desiccated thyroid administration, likewise, have been unsuccessful. On the other hand, it is easily prevented in rabbits. If 1 to 2 mg. of iodine are given weekly during the period of methyl cyanid administration no thyroid hyperplasia (goiter) develops and therefore no exophthalmos develops.

The most hopeful means of controlling the exophthalmos of Graves' disease at present available appears to be by prevention. By preventing goiter in general we will certainly lessen anterior pituitary stimulation and thereby lower the incidence of exophthalmos. This has already been proven in the state of Michigan where, following Kimball's introduction of goiter prevention about 1920, there has been a sharp decrease in the incidence both of endemic goiter and Graves' disease (McClure).

The only other general method of attempting the cure of exoph-

thalmos is by dividing the cervical sympathetic or removal of the cervical ganglia as introduced by Jaboulay,¹⁸ Jonnesco¹⁹ and others. Dividing the cervical sympathetic trunk only partially reduces the exophthalmos in rabbits, even in the earlier and uncomplicated stages. Removal of the superior cervical ganglion completely abolishes exophthalmos produced in rabbits by cyanid administration, at least during the first 2 or 3 months of its existence. It would probably be ineffective in the long-standing human cases where marked asthenia, degenerative and inflammatory changes have developed in the somatic muscles. If it were possible to divide the post-ganglionic fibers supplying the Mueller muscles only, the operation would be beneficial.

Summary. It may be stated that chronic and progressive exophthalmos can now be readily produced in immature animals of susceptible species by injecting pituitary extracts and by the injection of cyanids (preferably methyl cyanid) into rabbits maintained on a diet of alfalfa hay and oats. Both these means of production depend upon 2 factors: (1) upon the thyrotropic hormone of the anterior pituitary, in the one case by passively supplying it and in the other by stimulating the pituitary to produce it, and (2) upon the existence of a relative thyroid insufficiency. The maintenance of a normal thyroid by iodine or thyroxine administration prevents the cyanid and the pituitary extract exophthalmos. This indicates that normally there is a delicate physiologic balance between the thyroxine needs and the thyrotropic hormone. As regards therapy, iodine and desiccated thyroid appear to be the only logical remedies at present available but in neither the human Graves' disease nor in the experimental exophthalmos of rabbits are the results very promising.

The future outlook for controlling this deformity by prevention and even of curing individual cases, however, is far from hopeless. In the first place it can be prevented by iodine or by desiccated thyroid. In the second place it is our opinion that as the nature of Graves' disease is further unravelled it is quite probable that the natural cause (which we believe is due to a deficiency of some hormone of suprarenal cortex and gonad origin) of the stimulation of the midbrain centers occurring in Graves' disease which stirs the anterior pituitary to increased activity will be found and that a hormonal therapy may become available—a hormone probably of suprarenal cortex or gonad origin.²¹

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BOOK REVIEWS AND NOTICES.

TUBERCULOSIS IN THE CHILD AND THE ADULT. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P., Clinical Professor of Medicine (Department of Chest) University of Southern California, the School of Medicine; Medical Director, the Pottenger Sanatorium and Clinic for Diseases of the Chest, Monrovia, California. Pp. 611; 85 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, \$8.50.

THIS book encompasses in convenient bulk an adequate description, for the sanatorium physician or the physician in private practice, of the diagnosis and care of tuberculosis and the scientific principles on which these are founded. It is based on a comprehensive review of recent literature in the fields covered. The opening chapters present sociological considerations and the pathological background. The author holds to the view of endogenous reinfection, as the source of adult disease, which was the dominating view up to a few years ago, but he is conservative and gives consideration to the more recent belief, increasingly accepted in this country, of exogenous infection. There is a good exposition of the development, course and suitable treatment of childhood tuberculosis, with an enlightening set of Roentgen ray reproductions illustrating the resolution of childhood lesions. These would be improved if negative instead of positive reproductions were used. Elsewhere in the book superb negative reproductions, with the densities in white, are employed. The importance of the Roentgen ray in prognosis, as well as diagnosis, is well indicated. In general, physicians seeking sound information on the problems commonly encountered in the care of tuberculosis, will find their questions answered, and in conformity with other standard works on tuberculosis. Additional interest is given to this book by the extended consideration devoted to certain physiological principles, or in the author's term, the "Visceral neurology of tuberculosis," a field that has been largely developed by the author. The book is of great value for its concise assemblage of data on reflex symptoms and signs in tuberculosis previously recorded in a series of publications. In a final instructive chapter of 100 pages the diagnosis and treatment of a considerable variety of cases is illustrated by case reports from the author's experience.

E. L.

THAT HEART OF YOURS. By S. CALVIN SMITH, M.D., Sc.D. Pp. 212; 6 illustrations. Philadelphia: J. B. Lippincott Company, 1934. Price, \$2.

THIS book contains a description of the anatomy and physiology of the heart, and outlines the pathology, signs, symptoms and management of heart disease. It is written for the layman. It is not quite interesting enough in its style to be considered "light reading." It is more of the nature of a textbook. The reader may judge of the validity of the doctrine propounded from these quotations: "The eating of an excess of meat may produce a nephrosis of the kidneys." "The chemical formula of water is H_2O and this oxygen content is a valuable source of oxygen supply." "High blood pressure may be an indication that the individual is developing a resistance to an acute infection." "Sugar is a very powerful dynamic substance. In excess, it can so overwhelm the blood as to produce the coma (deep sleep) of diabetic shock. On the other hand, the diminution of sugars within the blood may so reduce the vitality that a form of sugar called glucose is employed by rectal injection to resuscitate the dying."

After describing the circulation of blood from the left ventricle through the aorta and arterioles to the capillaries, the author states: "Let us

continue with the return trip of vitiated venous blood to the heart. *En route*, the returning blood undergoes purification by passing through those filtration plants called the kidneys." The last chapter, "The Psychology of Reconstruction," is very well done. However, the rest of the book contains so many statements that are either inaccurate or debatable, that a doctor should read it himself before he suggests it for his patients' consumption. F. W.

ALCOHOL: ITS EFFECTS ON MAN. By HAVEN EMERSON, M.D., Professor of Public Health Practice, Columbia University. Pp. 114. New York, D. Appleton-Century Company, 1934. Price, \$1.

THIS is a brief résumé of the larger volume, *Alcohol and Man*, published in 1932 under the editorship of the author. It is intended for teachers in the public schools and for students in high school or college, to supply them with modern, authoritative information about a topic the social and economical importance of which is now even greater than ever before. The subject is treated concisely and factually and in non-technical words. The book may well be recommended by physicians to laymen seeking general information about alcohol. C. S.

NOTES ON THE MEDICAL TREATMENT OF DISEASE. By ROBERT DAWSON RUDOLF, C.B.E., M.D. (EDIN.), F.R.C.P., Professor of Therapeutics in the University of Toronto; Consulting Physician, Toronto General Hospital, and Victoria Hospital for Sick Children, Toronto, etc. Pp. 540. Fourth edition. Toronto: The University of Toronto Press, 1934. Price, \$4.

THE popularity of this little book, as shown by its reaching the fourth edition, is well deserved. Elementary though its scope, its science is sound and it so well seasoned with that which is the art of medicine that it should be particularly useful to the medical student and the young practitioner. R. K.

LE BARBITURISME AIGU ET LES ANTIDOTISMES GARDENAL (STRYCHNINE, CORAMINE, ALCOÛL) (ACUTE BARBITURATE POISONING AND ANTIDOTES FOR PHENOBARBITAL—STRYCHNINE, CORAMINE, ALCOHOL). By G. CARRIÈRE, Professor of the Medical Clinic of the Hôpital St.-Sauveur, Lille; CLAUDE HURIEZ, Chief of the Medical Clinic; and P. WILLOQUET. Pp. 164; illustrated. Lille: A. Durant, 1934. Price, 30 francs.

THIS monograph deals mainly with the clinical literature on acute barbiturate poisoning (its symptoms, signs, prognosis and pathology) and with a small series of animal experiments in which electrocardiographic tracings were made, the above-named antidotes were tried, and postmortem studies were made of the pathologic lesions. In view of the growing frequency of poisoning by drugs of this group, a publication of this nature would be welcomed by clinicians, but this one is not critical or comprehensive enough to satisfy the need. Nevertheless, it points out certain characteristics of human barbiturate poisoning that are not generally appreciated: fever, usually on the second day; oliguria or anuria, which may persist and cause death from uremia; myosis; pulmonary congestion, pneumonia, acute pulmonary edema; and a large variety of skin lesions, although these are less frequent in acute poisoning than in chronic. The dangerously toxic doses for man are given as 4 gm. of barbital, 3 gm. of phenobarbital, about 7 gm. of dial. In rabbits phenobarbital character-

istically caused congestion and fatty degeneration in the liver and an acute tubular nephritis; the lesions were not modified by treatment with strychnin. Authors' experience with strychnin as an antidote leads them to doubt that a quantitative antagonism exists between it and barbiturates; although it was of some benefit, it did not cause more rapid recovery and it often caused violent convulsions in the midst of phenobarbital coma. They believe coramin is a more promising antidote, but alcohol (30% intravenously) seems best of all. No explanation for this extraordinary effect of alcohol is offered, nor is there any mention of the dangers (thrombosis or embolism, hemolysis, cardiac depression) of intravenous injection of 30% alcohol: it had not been tried on human beings at the time of writing.

C. S.

AN INTRODUCTION TO PRACTICAL BACTERIOLOGY. A Guide to Bacteriological Laboratory Work. By T. J. MACKIE, M.D., D.P.H., Professor of Bacteriology, University of Edinburgh, etc., and J. E. McCARTNEY, M.B., D.Sc., Director of Research and Pathological Services, London County Council, etc. Pp. 504. Fourth edition. Baltimore: William Wood & Co., 1934. Price, \$4.

THIS might well be called a handbook of bacteriology. It will prove a valuable aid to the laboratory technician as a clear, concise presentation of the essential routine procedures. The fourth edition with its exposition of improved cultural methods has a place on the reference shelf of every laboratory. The novel presentation of bits of theory along with the technique increases its usefulness for the undergraduate student, and the book would serve very well as a laboratory outline for first courses in bacteriology.

D. L.

A SHORT HISTORY OF SOME COMMON DISEASES. By DIVERS AUTHORS. Edited by W. R. BETT, M.R.C.S. (ENG.), L.R.C.P. (LOND.), Late Resident Medical Officer, Princess Elizabeth of York Hospital for Children, Shadwell, E., etc. Pp. 211. London: Oxford University Press, 1934. (Price not given.)

THIS "original venture in medical literature" gives, entertainingly but compactly, the important details in the development of knowledge of more than a score of the commoner diseases. The names of such well-known writers as Broadbent, John Fraser, d'Arcy Power, Humphrey Rolleston, R. O. Moon, J. D. Comrie and others guarantee the accuracy of the presentation. One regrets that apparently limitations of space have at times led to a rather categorical listing of events in a book that one would like to have seen twice as large.

E. K.

NEW BOOKS.

International Clinics, Vol. 3, Forty-fourth Series, 1934. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 collaborators. Pp. 327; illustrated. Philadelphia: J. B. Lippincott Company, 1934.

Items of especial interest in this number are the two opening articles on the heart with an excellent colored plate of cardiac cyanosis, a short but illuminating statement of a concept of allergy, and an interesting clinicopathologic conference.

- Practical Talks on Heart Disease.* By GEORGE L. CARLISLE, M.D., Associate Professor of Clinical Medicine, Baylor University, Dallas, Texas. Pp. 153. Springfield, Ill.: Charles C Thomas, 1934. Price, \$2.00.
- The Compleat Pediatrician.* Practical, Diagnostic, Therapeutic and Preventive Pediatrics. By WILBURT C. DAVISON, M.A., D.Sc., M.D., Professor of Pediatrics, Duke University School of Medicine, and Pediatrician, Duke Hospital. Unpaged. Durham, N. C.: Duke University Press, 1934. Price, \$3.75.
- Parasitism and Disease.* By THEOBALD SMITH, Director Emeritus of the Department of Animal Pathology, Rockefeller Institute for Medical Research. Pp. 196. Princeton, N. J.: Princeton University Press, 1934, on the Louis Clark Vanuxem Foundation. Price, \$2.00.
- The Surgical Clinics of North America.* Vol. 14, No. 4 (Chicago Number—August, 1934). Pp. 288; 88 illustrations. Philadelphia: W. B. Saunders Company, 1934.
- Pathologie der Mitose.* By GEORG POLITZER, Privatdozent der Embryologie an der Wiener Universität. Vol. 7 of Protoplasma-Monographien. Pp. 238; 113 illustrations. Berlin: Gebrüder Borntraeger, 1934. Price, Rm. 16.20.
- The Cyclopedia of Medicine, Vol. 10.* GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief, and EDWARD L. BORTZ, M.D., Assistant Editor; Chief Associate Editors, W. WAYNE BABCOCK, A.M., M.D., CONRAD BERENS, M.D., P. BROOKE BLAND, M.D., FRANCIS L. LEDERER, B.S., M.D., A. GRAEME MITCHELL, M.D. Pp. 1167; illustrated with half-tone and line engravings, also full-page color plates. Philadelphia: F. A. Davis Company, 1934.
- Epidemic Myalgia.* Bornholm Disease. By EJNAR SYLVEST, M.D. With a Foreword by DR. TH. MADSEN, Director of the Danish State Serum Institut, Copenhagen. Translated from the Danish by Hans Anderson, M.D. Pp. 155. Copenhagen: Levin & Munksgaard, 1934. Price, D. Cr. 8.—.
- Die Werke des Hippokrates.* Part 5. Die Winde/Die Heilige Krankheit (Price, Rm. 1.50). Part 14. Die Hippokratischen Lehrsätze (Price, Rm. 2.10). Pp.: Part 5, 65; Part 14, 80. Stuttgart: Hippokrates-Verlag G.M.B.H., 1934. (To be published in 25 parts, costing ca. Rm. 100, card binding.)

NEW EDITIONS.

- A Text-Book of Pathology.* Edited by E. T. BELL, M.D., Professor of Pathology in the University of Minnesota, Minneapolis. Pp. 767; 364 illustrations and 2 colored plates. Second edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$8.50.
- In the revised and enlarged second edition, many new references and a chapter on diseases of the bones and joints (by Bell) have been added. The good features noticed in our review of the first edition (*Am. J. Med. Sci.*, 181, 420, 1931), are still present and some shortcomings have been removed. The book continues to be an authoritative statement of the essentials of pathology, with more satisfactory, extended treatment of a few sections.
- The Autonomic Nervous System.* By ALBERT KUNTZ, Ph.D., M.D., Professor of Micro-Anatomy in St. Louis University School of Medicine. Pp. 697; 73 illustrations. Second edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$7.50.
- A Textbook of Histology.* By ALEXANDER A. MAXIMOW, Late Professor of Anatomy, University of Chicago, and WILLIAM BLOOM, Associate Professor of Anatomy, University of Chicago. Pp. 662; 530 illustrations, some in colors. Second edition, completely revised. Philadelphia: W. B. Saunders Company, 1934. Price, \$7.00.

PROGRESS OF MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,
PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,
SURGEON, JEWISH HOSPITAL, PHILADELPHIA.

VAGINITIS.

Before attempting to study pathologic lesions of any part of the body it is always well to have a knowledge of the normal histology and physiology of that part. Therefore, some studies on the biology of the vagina are presented.

Varying Vaginal Flora.—Cruickshank and Sharman¹ have observed the bacterial flora and secretions of the vagina at all ages from birth until after the menopause and also during pregnancy. In the virgin there are 4 alternating phases: (1) Soon after birth and for the first 2 or 3 weeks of life simple homogeneous flora of Gram-positive bacilli, known as Doederlein's vaginal bacillus, are established in the vagina in association with a highly acid non-purulent secretion. (2) After the first month and until puberty, vaginal bacteria are sparse and varied while the secretion is scanty or absent and when measurable, is alkaline in reaction. (3) At puberty there is a reversion to the type of flora and secretion found in the first week of life, a condition apparently persisting in the healthy woman until the menopause. (4) Following the menopause, there is a return to the sparse flora and scanty alkaline secretion found in the vagina before puberty. These findings correspond closely with the authors' previous studies on the presence or absence of glycogen in the vaginal epithelium. When glycogen is present, as in the newborn infant and during the reproductive period, the homogeneous bacterial flora and highly acid secretion appear. When it is absent, the secretion is scanty and alkaline and the bacterial flora usually are varied. Obviously the glycogen is being utilized with the consequent production of acid which soon reaches such a concentration that only acid-resistant bacteria, such as Doederlein's bacillus, can survive and multiply. In this way a defense mechanism is produced in the vaginal

cavity capable of preventing the establishment there of foreign or harmful bacteria.

Since the Doederlein bacillus is normally present in the vagina during the reproductive period, Mohler and Brown² have used cultures of this organism in the treatment of vaginitis in a small series of cases with encouraging results. The culture, grown in whey, is prepared by mixing $\frac{1}{2}$ ounce with enough sugar of milk to make a thin paste. The mixture is implanted in the vagina after cleansing with dry cotton and a small cotton tampon is then placed in the vaginal introitus. The treatment is repeated once daily either by the physician or patient. After a cleansing douche of plain water, the mixture is injected into the vagina with a soft rubber ear syringe, the patient assuming a reclining position with the hips elevated. Smears of the vagina are made weekly until the Doederlein bacillus can be recovered by culture. All of the patients in this series complained of a leucorrhea which had failed to respond to other methods of treatment, such as cauterization of the cervix and Skene's tubules and the application of antiseptics following thorough cleansing of the vagina. The Doederlein bacillus was absent in every case before treatment was begun. Proof of cure was based on absence of symptoms, the inability to find pus cells in large numbers in stained smears, failure of the vaginitis to return after treatment has been discontinued and finally recovery of cultures of the implanted organisms from the vagina.

Trichomonas Vaginalis Vaginitis.—In recent years much consideration has been given to trichomonas vaginitis. While the disease is frequently found, it is often refractory to all of the numerous treatments advocated. As the organism is a protozoön and as quinin is known to destroy some of the protozoa, it occurred to Sure and Bercey³ that quinin might be useful in the treatment of such cases. In their small series of 7 cases all have been improved clinically and microscopically by the use of quinin, although 6 of the patients had previously received various treatments without improvement. The treatment consists of the insufflation of 15 grains of quinin sulphate powder into the vagina with a powder blower daily for a few days, checking the effect of the drug on the organisms which as a rule soon disappear. In some cases this was supplemented by the use of 15-grain quinin capsules which the patient inserted into the vagina at night. Under the microscope it was found that when quinin was brought in contact with trichomonads they were immediately thrown into spasm followed by diminishing motility with complete cessation in a short time.

The treatment advocated by Goodall⁴ consists of the use of an acid antiseptic in a medium which will slowly dissolve thereby keeping the vagina in a constant bath of antiseptic. These two factors are obtained by using vaginal cones of 1% picric acid. A cone is inserted high up in the vaginal vault on retiring. A lactic acid (1 dram to the quart) douche is taken daily in the morning. After the first treatment with the cone the whole vagina is stained a pale yellow. There is usually a tendency to recurrence following menstruation, but this may be controlled by the above treatment, in fact the treatment may be continued throughout menstruation. His results have been successful in a series of 64 cases in from 5 to 10 days. The pruritus disappears during the

first 3 treatments and the pus is generally absent on the 3d or 4th day. Desquamation goes on for some time but by the 10th day the mucosa has taken on a healthy appearance. The treatment may be given during pregnancy except during the last month.

The method of Ruble⁵ is based on the principle of osmosis. The trichomonas has a semipermeable cell wall which encapsulates a fluid or semifluid protoplasm. Theoretically a rapid increase in salt concentration in the fluid surrounding the trichomonas should result in its destruction, in the process of establishing osmotic equilibrium. Corroborating this theory by laboratory experiments, Ruble then applied it clinically by having the patients insert 2 magnesium sulphate suppositories (75 grains each) into the vaginal vault night and morning for 3 days and then 2 each night for the next 3 days. On the 7th day there are few pus cells remaining and usually no organisms. If organisms are still present either the amount of magnesium sulphate is increased or copper sulphate suppositories (5 grains) are substituted. Subsequent treatment consists of one suppository nightly until the next menstruation when 2 are inserted each night during the flow. If no organisms are present after the flow, the suppositories are continued every other night during the second month. All treatment is discontinued at the end of the second period, if examination shows no organisms.

Smith⁶ treats these patients by the use of a suspension of $\frac{1}{2}$ teaspoonful of sodium perborate powder in a half cup of lukewarm water. In the recumbent position the patient gently injects this freshly prepared suspension into the vagina night and morning and continues the treatment during menstruation. In 2 or 3 days the patient experiences marked relief from symptoms and as a rule speaks of a great lessening of the vaginal discharge. It is his practice at the first examination to instil into the vagina a small amount of 5% mercurochrome on a sponge. If the routine is continued for 1 or 2 months or through 1 or 2 menstrual periods, the patient may stop all treatment and be free from symptoms. The basis on which this treatment is founded is that in cultures the trichomonas is found at the bottom of the test tube and also multiplies under true anaërobic conditions. Furthermore increased oxygen tension is toxic for a number of parasitic species of trichomonads. Sodium perborate when in contact with exudates gives off bubbles of oxygen, though more slowly than hydrogen peroxid.

According to Ayer and Neil⁷ trichomonas vaginitis yields readily to treatment based upon the fact that trichomonas vaginalis requires an environment which is acid in reaction. For 5 years they have had unvarying success in the treatment of this disease by a simple form of treatment. Bicarbonate of soda is given by mouth until the urine is alkaline, usually giving 2 or 3 teaspoonfuls daily. After thoroughly cleaning and drying the vagina and cervical canal, the lower cervical canal is packed with powdered sodium bicarbonate and then about 2 ounces of the bicarbonate is packed into the vagina as the speculum is withdrawn. The patient takes a douche the following day using 1 to 2 ounces of soda bicarbonate to 1 quart of warm water and assuming the recumbent position. The "soda pack" gives a burning sensation which lasts for 3 to 5 hours but most women are willing to endure it without sedatives. Relief from burning on urination and vulval irritation occurs within 24 hours from the institution of treatment. Treat-

ments are given on alternate days until the parasites disappear, after which the douches alone are continued until after the second menstrual period. If the patient is then microscopically negative, treatment may be discontinued.

It might be well to call attention to the fact that, in the opinion of some investigators, the *trichomonas vaginalis* has very little if any etiologic relationship to vaginitis. Thus Hibbert⁸ states that it may be found in the vaginal secretions of many women for long periods of time without producing vaginitis. On the other hand in a large percentage of cases having an acute vaginitis where the *trichomonas* exists, there is an associated predominant growth of a Gram-positive, nonhemolytic, short-chain streptococcus present which is capable of producing an active vaginitis when not associated with the *trichomonas*. He has found that by repeated vaginal applications of a specific streptococcic bouillon filtrate the active growth of the organisms in the vagina ceases and the vaginitis subsides in spite of the persistence of the protozoön in the secretions. After describing the method of preparation of the bouillon filtrate he states that the method of treatment was uniform. All other methods of treatment were suspended, all douches forbidden and the patient was allowed 1 tub bath daily. In indicated cases repeated cauterization of the cervix was resorted to where cervicitis was present. The vaginal canal was dried with sterile cotton and a large cotton tampon saturated with the bouillon filtrate was packed against the cervix and allowed to remain in place for 12 hours during which time the patient was advised to remain off her feet in order to aid in retaining the fluid in the vagina. The treatment is repeated 2 or 3 times a week until the vaginitis disappears.

Another line of reasoning concerning the rôle of the *trichomonas* is that suggested by Hesseltine⁹ who states that it is well established that patients suffering from *trichomonas* vaginitis are prone to have recurrences, especially at or following the menses. It is equally known that exacerbations of gonorrheal cervical infections are often related to the menstrual period. By analogy one might argue that the etiologic agents in "*trichomonas* vaginitis" were bacteria with their foci in the deeper vaginal epithelium or in the cervical glands. Such infections present difficulties in effecting prompt and consistent cures. The most conclusive study in determining pathogenicity of vaginal flagellates would involve freeing the trichomonads from all bacteria, fungi and other infective agents and transplanting them into the vaginas of uninfected women and then being able to recover and identify the organisms after the disease has developed. If strict isolation proves impossible, proof of pathogenicity must rely upon indirect evidence, such as the production of the disease by bacteria commonly associated with the parasites, with the demonstration of the relationship between the bacteria and the trichomonads. Finally it may be shown that neither the flagellates nor the bacteria by themselves are pathogenic, but that one group activates the other. While he believes that "*trichomonas* vaginitis" is produced by some infective agent, he feels that the pathogenicity of the *trichomonas vaginalis* has not been proved conclusively. He states that it would seem that the *trichomonas* is a scavenger and feeds upon bacteria; furthermore it fails to grow on

media in the absence of bacteria, so that presumably an abnormal vaginal flora is a prerequisite for the invasion of the trichomonads.

During pregnancy the presence of the trichomonas may be a very annoying complication. In the Cook County Hospital, Chicago, Crown¹⁰ examined 300 patients during the 9th month of pregnancy and found the trichomonas vaginalis in 50 of 200 white women and in 50 of 100 colored women. The incidence was much greater in nulliparæ than in multiparæ although age is an irrelevant factor. The large majority of the patients had no complaints relative to the presence of the organism. The trichomonas may be found in any kind of discharge but the characteristic type is thin, yellowish and foamy. It does not cause abortion nor increase puerperal morbidity and causes no difficulty in labor unless there is an associated vaginitis.

In the treatment of trichomonas vaginalis vaginitis during pregnancy Glassman¹¹ has tried many of the numerous methods recommended but at present advises the use of pure crystallin phenol in an acid medium, notably boric acid powder, instead of the usual sodium bicarbonate, as he found that the sodium bicarbonate often produces an irritation. Essential oils are added for their cooling effect. In acute cases the patient is allowed to take daily douches for 1 or 2 weeks which relieves the symptoms and allays the irritation. The vagina is then swabbed with a cotton pledget and the dry powder, mixed with 3 times its volume of boric acid powder, is instilled into the vagina, the patient being instructed to take a douche with warm water the same evening or the next morning. As the phenol content of the douche powder averages from 6 to 8%, it must be mixed with at least 3 times its volume of boric acid powder before it is used dry in the vagina. In a number of patients who harbored the organisms during pregnancy and had no treatment, a spontaneous cure occurred during the puerperium. In 2 cases they remained free from infection until they again became pregnant when the organisms returned.

Trichomonas vaginalis vaginitis in childhood is most unusual, in fact it has been said that the organism has never been found before the onset of menstruation. Whether this has anything to do with the biologic condition of the vagina as outlined in the beginning of this review cannot be definitely stated but it is suggestive. Frankenthal and Kobak,¹² however, report 4 cases of trichomonas vaginalis vaginitis during or before puberty. Three of the patients were prepubescent and the other had had only one menstrual period. They found that the local treatment in children is very difficult and unsatisfactory because of the virginal introitus and the infantile state of the genitals. Improvement of local and general hygiene together with a well balanced diet is very beneficial and the 1 patient in this series who was limited to these measures made the most satisfactory progress. The course of this infection in childhood is quite prolonged and it is more difficult to effect a cure than in adults.

Gonorrheal Vaginitis.—The diagnosis of gonorrheal vaginitis is sometimes surrounded with difficulties and in cases of a medicolegal character may be quite hazardous. In a series of 500 consecutive cases at the London County Council clinic at Whitechapel, reported by Mascall,¹³ no case was labeled as gonorrhea unless and until pathologic

tests proved the presence of the gonococcus; clinical observations alone were considered insufficient. Cultures produced the highest number of positive results (66.8%). The value of the gonococcus complement-fixation test is second (58.6%), but the corrected figure when the latest technique is used, places this test first with 79.6% positive results. It has a definite place among the diagnostic methods of gonorrhea; but the clinical history and condition must be carefully considered when interpreting the results. In many cases it is indispensable as 142 cases (20.8%) were discovered which otherwise would not have had their true nature revealed. Smears alone, even when stained with Gram's stain, give poor results (45.4%), which is even worse if only methylene blue is used. Whenever possible the three methods should be combined as the results from one method alone may not be dependable.

Gonorrheal Vulvovaginitis in Children.—Schauffler and Kuhn¹⁴ state that the gonococcus requires a "harbor of infection" for its growth and the development of its pathogenic characteristics. In exposed locations it becomes impotent and perishes. Only in the deep recesses such as the glands of Skene and Bartholin, cervical glands or the plicæ of the tubes does this organism find its ideal habitat. Its pathogenic action on the genital apparatus of children is not due to changes in bacteriologic properties or low resistance of the invaded tissues, as has often been stated, but is due to mechanical and developmental differences between the immature and the mature female genitalia. Since the rudimentary Skene's and Bartholin's glands of immature individuals offer no harbor of infection it is not to be expected that infection of clinical importance will occur. Similarly the immature endocervix is practically never infected by the gonococcus because the cervical glands are not present in a form to harbor the organisms and on this account a high degree of immunity is granted to the endometrium and Fallopian tubes. On the other hand the contracted rugose vagina of the immature individual constitutes an ideal harbor of infection and explains the occurrence of a primary vaginitis as the most usual manifestation of gonorrhea in the immature individual. In the adult, the distention and flattening of the vaginal wall with the frequent introduction of bacteria entirely alters the conditions favorable to the development of this organism. From this it may be seen that the most effective means of treating gonorrheal vaginitis in children is achieved through the use of a relatively firm ointment base, injected by a technique which insures the production of sufficient intravaginal pressure to cause the invasion of the ointment into every crypt and corner of the rugose vagina. They advise the use of 1% silver nitrate incorporated in plain anhydrous lanolin. The ointment should not be warm as its quality of firmness facilitates distention of the vagina with the use of mild intravaginal pressure. Furthermore it is more easily and completely retained if cold and has the highest possible affinity for fluids, which makes it a highly effective vehicle for carrying the antiseptic into the moist vaginal wall, in contrast to the usual petrolatum base which is repulsed by moisture. This article is illustrated by Roentgen ray pictures which are very convincing as to the length of time such an ointment will remain in the vagina. (Years ago Gellhorn

of St. Louis suggested the employment of 1% silver nitrate in a more or less solid base and reported good results from same. Moderately good results from this treatment have also been secured by one of the editors—C. C. N.)

In contrast to the above comparatively simple treatment, Peterson¹⁵ details the method which he has found to be efficient. A 1 to 1000 solution of acriflavin hydrochlorid is injected into the urethra until the urine is repeatedly free from pus. The entire vulvar mucous membrane is painted with a 2% solution of mercurochrome and then the vagina is filled with an ointment of 1% mercurochrome in equal parts of vaseline and lanolin and a light pad and T bandage is applied to retain the ointment. A hot sitz bath is given daily for 15 to 20 minutes and the pelvis is baked in carbon lamp appliances from $\frac{1}{2}$ hour to 1 hour daily. Potassium permanganate douches (1 to 10,000) are given if the discharge is excessively purulent or offensive. Silver nitrate is applied to the urethra and vagina twice a week after the first month's treatment. The hymen is incised when necessary to procure efficient drainage. The cervix is inspected through an endoscope and when found to be affected is treated with a 2% solution of acriflavin, 5% mercurochrome or from 2 to 5% solution of silver nitrate. After a month of routine treatment gonococcus mixed vaccine is given in 4 injections: first dose, 0.15 cc.; on 3d day, 0.2 cc.; on 6th day, 0.25 cc.; on 10th day, 0.3 cc. Cod-liver oil is given 3 times daily during the winter months. When 3 or 4 smears are negative for pus as well as for Gram-negative cocci the children are put under observation for 2 or 3 weeks, during which time they are examined every other day until discharged from the hospital after which they are examined every 2 weeks for 2 to 3 months.

While practically all types of treatment of this disease are based upon the use of local antiseptic applications in one form or another, a radically new method of treatment has been suggested by Lewis¹⁶. It is generally conceded that the gonococcus is a highly selective organism able to exist only in certain tissues. Furthermore vulvovaginitis subsides before the changes of puberty have converted the delicate thin layered epithelium lining the child's vagina to the thicker structure of the adult, in fact, primary infection of the adult vagina is either extremely short-lived or non-existent. With these facts in mind the thought occurred to him that if one were able to change the character of the epithelial lining of the child's vagina, one might reasonably hope to destroy the invading gonococcus by making its habitat unfavorable. Accordingly he began to treat children having gonococcus vaginitis with theelin, the female sex hormone which is responsible for the sex development of the female at the time of puberty. The treatment has been carried out on 8 children with typical severe vaginal infections. No other form of treatment was employed while theelin was being given. The vulvar surface only was sponged with salt solution when it became fouled with vaginal secretions. Four of the patients presented themselves with recent untreated infections, the remainder gave histories of a gonorrheal vaginitis of from 6 to 20 months' duration. In none of these had treatment been given during the 3 weeks preceding the administration of theelin. No local irritation resulted from the administration of theelin nor were there unfavorable general symptoms. The children receiving larger amounts of theelin exhibited hypertrophy

and increased vascularity of the labia majora and minora and of the introitus which resembled the conditions found in the newborn child. In no case did uterine bleeding result from or follow the treatment. During hospitalization of the patients vaginal smears stained by Gram's method were examined in some instances daily, in others every 3 or 4 days. In the majority of the cases vaginal discharge ceased in 1 to 3 weeks after treatment was instituted. At the conclusion of treatment the discharge was absent in all 8 cases and smears were negative for gonococci. Desquamation of epithelial cells in large numbers was usually found in 7 to 21 days, in several instances being so great that cheesy or scaly plugs were extruded from the vagina. In the earlier cases a bit of the lateral wall of the vagina, 3 to 4 cm. above the hymen was removed for microscopic examination before and after theelin injections. For this purpose a miniature tonsil punch was introduced through a peculum, a procedure which caused little pain and proved harmless. Normal control sections were also obtained at autopsies from the vaginas of children of different ages. The normal child's vagina is lined with delicate squamous epithelium 4 to 6 layers in depth. In contrast, the injection of theelin induces in 10 or more days an enormous thickening of the epithelium, there being from 25 to 35 or more layers of vacuolated cells superimposed upon the basement layer. He has found that small doses of theelin given at short intervals are more efficient than larger doses given infrequently and he plans to test the effect of frequent oral administration of the hormone so as to develop a method of therapy more suitable for use in the home. He particularly emphasizes that until the proper dosage of the hormone and the possible deleterious effect of its administration is understood, it should be employed with caution. In his work all the patients received daily either 1, 2 or 3 hypodermic injections of 50 rat units of theelin in the arm or leg.

This work of Lewis has been corroborated by Brown¹⁷ who treated 7 patients who had been receiving other forms of treatment without results 2 or 3 times a week for months and years. He gave daily doses of theelin varying from 50 to 100 units. The smears became negative in 10 days in half the cases and were negative in all of them by the end of 30 days. He also found that none of the children had vaginal bleeding nor any constitutional reactions, while in only 1 did he notice any marked turgescence of the labia and very slight enlargement of the breasts, that child being the youngest in the series and had received the largest number of injections as well as the largest total amount of theelin. These results, which seem to be based on sound biologic principles, offer the hope that this distressing disease may soon be conquered by a relatively short and simple form of treatment.

Vulvovaginal Diphtheria.—According to the literature as reviewed by Wallfield and Litvak¹⁸ vulvovaginal diphtheria in children is rare but should be considered as serious an involvement as the faucial or pharyngeal forms. The clinical picture varies from a mild infection to one of a severe nature with cutaneous gangrene. A gray membrane may form on the inner surfaces of the labia and extend from there to the surrounding structures. All the tissues involved are red, swollen and extremely painful. A fetid vaginal discharge may be present and

the inguinal glands are swollen and tender. Small ulcerations may remain for some time after the disappearance of the membrane. All cases have marked dysuria and pain on walking or moving the legs but there may be no fever. Toxin absorption seems to be slower from the vagina. Local treatment does not seem to hasten negative cultures and it is debatable whether it is of any benefit, although general hygienic cleaning is permissible. They report a case with extension of the membrane across the perineum to the anal region which was treated with antitoxin 20,000 units intramuscularly and 10,000 units intravenously. Although positive cultures were obtained from the nose, throat, vulva, vagina and anal regions, rapid healing of all lesions followed serum therapy.

F. B. B.

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DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

COÖPERATIVE CLINICAL STUDIES IN THE TREATMENT OF SYPHILIS.

ONE of the most outstanding contributions to the field of syphilology in recent years has been a coöperative study originally undertaken by the health section of the League of Nations in which five American clinics participated in an investigation of a study of treatment results in early syphilis and in syphilis associated with pregnancy. These

clinics have extended the original study to include a retrospective inquiry into the results of treatment in various other aspects of syphilitic infection. The clinics and their directors were: the University of Michigan (Udo Wile), the Mayo Clinic (Paul O'Leary), Western Reserve University (H. N. Cole), the University of Pennsylvania (J. H. Stokes) and the Johns Hopkins University (J. E. Moore), in association with the United States Public Health Service (Dr. Thomas Parran, Jr., and subsequently Dr. Taliaferro Clark, Assistant Surgeon Generals in charge of the Division of Venereal Diseases, and Lida J. Usilton, Associate Statistician).

The expense of the undertaking was borne by a generous grant from an anonymous donor and subsequently by the Milbank Memorial Fund and the United States Public Health Service. The accumulated, pooled clinical material approximated 75,000 records of patients treated for syphilis and, while individual directors were responsible for the study of certain phases of the problem and for the conclusions reached in their individual studies, all data were submitted to the entire Group for revision and approval prior to publication. All patients had been treated by relatively modern methods and had to be under observation and treatment for not less than 6 months to be included. The aims and plan of the investigation are discussed in detail in *Venereal Disease Information*, 13, 135, 1932. It will not be possible to abstract here all the conclusions reached in a study approaching monographic proportions so far published, but an attempt will be made to summarize the most.

Early Syphilis, Clinical Manifestations and Diagnosis. Stokes as spokesman for the Group¹ has reviewed a material of 3244 cases of early syphilis including 342 patients with seronegative primary, 585 with seropositive primary, 2252 in the early secondary phase (lesions developing within the first year of infection) and 65 with late secondary syphilis (lesions developing after the first year). It was found that positive darkfield examinations were obtained in 94.4% of seronegative primary syphilis; 90.7% of the genital lesions of secondary syphilis in which a darkfield examination was made; 85.6% in mouth and throat lesions, and 79.3% in cutaneous lesions, including condylomas. Darkfield equipment can therefore be advantageously used in the diagnosis of secondary lesions. Of the total of 3244 early syphilis patients, 10.5% appeared in the seronegative primary stage; 70.4% in the secondary stage with positive blood Wassermann reaction. The blood Wassermann reaction was negative in secondary syphilis in 1% of patients. Alopecia is more frequent in white females than in white males; twice as frequent in the white as in the colored females. Mucosal secondary lesions other than condylomas are 10% more common in white than in colored patients. Condylomas are more frequent in women than in men. Colored females stand much higher than any other type in this particular; suppression of infectiousness in the colored woman is therefore especially important.

Neurosyphilis was clinically recognizable in 1.7% of 2269 patients with early secondary syphilis before treatment was begun; in all cases, an acute syphilitic meningitis with or without cranial nerve palsies. This type of neurosyphilis yields readily to treatment. Of 1747 patients with spinal fluid tests, the fluids were completely normal in 67.3%;

abnormal in 32.7% without reference to the time of the secondary period at which the test was done. The increased cell count is the most frequent abnormality; a specific warning against the practice from the interpretative standpoint of reporting only the Wassermann test on a spinal fluid. Early asymptomatic neurosyphilis as indicated by cerebrospinal fluid examination regardless of time performed or previous treatment occurs in 23.8% of seronegative primary, 29.8% of seropositive primary, 34.1% of early secondary, and 56.1% of late secondary patients. There is a definite relationship between spinal fluid abnormality and the blood Wassermann reaction; the more marked the fluid abnormalities, the more likely is the blood Wassermann to be positive. More than 40% of those whose fluids show a positive Wassermann test, among other abnormalities, are Wassermann fast. The failure of the blood Wassermann reaction in early syphilis to respond in the first 6 months of treatment is an intimation of the presence of asymptomatic neurosyphilis.

Of the 3244 patients, 2.8% had eye complications on admission. Iritis and uveitis form 73.3% of the eye complications; neuroretinitis, 11.1%; keratitis, 11.1%. Colored patients present eye involvement more than 3 times as frequently as white patients, and females have eye lesions oftener than males in both races.

Results of Treatment in Early Syphilis. Stokes² found that in a group of 2889 patients with early syphilis satisfactory results, including "cure," are obtained in the following proportions of cases, dependent on the stage of the disease at which the treatment is begun: Seronegative primary, 27.5%; seropositive primary, 23.2%; secondary, first year, 18.4%; secondary, delayed, 29.2%. This represents a superiority of curative outlook of about one-third when treatment is begun in the seronegative primary stage. Relapse and resistiveness to treatment are also less marked in patients beginning treatment in the seronegative primary stage: 13.2%, as compared with 27% in seropositive primary syphilis, 27.8% in secondary syphilis, and 40% in delayed secondary syphilis.

From the material the statement can be made with almost axiomatic force that continuous treatment, whether prolonged or brief and practically regardless of the drugs used, is superior in its results to intermittent or other schemes of treatment. Continuous and intermittent treatment are in their turn both superior to so-called "intensive" treatment (very short arsphenamin courses); and irregular treatment stands throughout the studies as inefficient, productive of relapse and progression, fixed positive serologic tests and unsatisfactory treatment outcomes. At certain points, intensive is little better than irregular treatment. Among cases treated with arsphenamin alone, the continuous method secured the reversal of the blood Wassermann reaction by the end of a year in 91.2%, whereas the intermittent scheme of treatment, with arsphenamin alone and rest intervals of a month or more, secured only 58.5% of reversals, and irregular treatment with arsphenamin alone secured only 9.3% of Wassermann reversals to negative within a year.

There is a definite relationship between resistant positive serologic tests and the tendency to clinical relapse. The total of relapses in

patients always negative or reversed to negative within the first year is only 22.5%, as compared with 48.1% in patients whose tests showed delayed reversal. This statement holds good for any scheme of treatment and for each type of relapse. Sixty per cent of patients undergoing permanent serologic reversal to negative under treatment do so in less than 6 months and 40% in more than 6 months. In the vast majority of cases, failure to secure satisfactory serologic results lies at the door of the rest interval or irregular treatment, rather than any peculiarity of disease or patient.

The factors underlying the fixed positive Wassermann reaction include (1) the stage of the disease at which treatment is begun, difficulty being experienced much more frequently in seropositive primary, secondary and delayed secondary cases than in seronegative primary cases; (2) the occurrence of lapse from treatment from whatever cause. The effect of treatment on the spinal fluid findings is as follows: Slightly abnormal spinal fluids (cell count above 6, increased globulin) is good, whether treatment be much or little. A much greater resistance attaches to greater degrees of abnormality, including the presence of the paretic formula, which type of fluid is much more difficult to reverse than any other markedly abnormal fluid. Of the total number of patients examined, 1.3% proved to have irreversible spinal fluids (42 cases), which is 5.8% of the 730 abnormal spinal fluids.

Early mucocutaneous relapse occurred in 15% of those who received little arsphenamin (that is, 19 or less injections) and in only 2% of those who received 20 or more injections. Central nervous system syphilis is almost 3 times as common in those who received little as in those who got much arsphenamin. Late syphilis as relapse, excepting cardiovascular syphilis, is entirely absent from the "much arsphenamin" group. Progression in the cardiovascular system, however, occurs approximately as frequently in those who receive much as in those who receive little treatment. No evidence appears from the statistical analyses that mass of treatment is in any way injurious to the patient with respect to the outcome of his infection.

Continuous treatment with arsphenamin in preference to neoarsphenamin is the optimum procedure. The weaknesses of neoarsphenamin from the standpoint of its ability to bring about serologic reversal are in part compensated by the use of a heavy metal, and the disparity between the two drugs tends to disappear as the treatment becomes intermittent or irregular. Neoarsphenamin cannot, however, be rated as an ineffective drug. Comparisons between arsphenamin-mercury and arsphenamin-bismuth treatment disclose the latter as the more effective in ultimate results, mucocutaneous relapse occurring in 9.6% of cases with arsphenamin-mercury and 3.6% of cases with arsphenamin-bismuth. Within the first 3 months of treatment the percentage of patients securing Wassermann reversal is practically identical with both bismuth and mercury, whether used with arsphenamin or neoarsphenamin, but with longer treatment (4 to 12 months) there appears to be a distinct advantage for bismuth over mercury with either arsphenamin or neoarsphenamin (41.5% reversals with arsphenamin-bismuth *versus* 29.7% with arsphenamin-mercury, and 39.8% for neoarsphenamin-bismuth *versus* 33.1% for neoarsphenamin-mercury).

Serologic resistiveness is a definite indication of early relapse of a

secondary type (mucocutaneous or ocular), for there were 25.5% relapses of this type among 1282 patients who were serologically resistant, as compared with 5% of 1962 patients with a more satisfactory Wassermann response. The tendency to relapse is vastly increased by intermittent or irregular treatment, with rest periods voluntary or involuntary; and the serologic resistance of the case is an indicator of relapsing tendencies. Relapse is more frequent in younger than in older patients. The notably greater tendency to mucocutaneous relapse when treatment is begun in seronegative primary stage demands increased, not decreased, treatment, or so-called "abortive cures," at this stage. With respect to complications of treatment in early syphilis appraised on a time-treatment basis, reactivity is high where much heavy metal is employed. It is not greatly increased even by vigorous arsenical treatment.

Although neoarsphenamin has the reputation of being less reaction-producing than arsphenamin, the proportion of serious to total reactions with the two drugs in this study stand as 13.4% for arsphenamin, as compared with 22.0% for neoarsphenamin.

The Treatment of Latent Syphilis. Moore³ was appointed by the Group to review the records of 1936 patients with latent syphilis (clinically non-recognizable syphilitic infection), the diagnosis resting on a positive serologic test or a clean-cut history of infection inadequately treated. The most noteworthy recent clinical advances in this field are the exclusion from the diagnostic category of latency, of patients with early cardiovascular syphilis (simple aortitis), and of patients with asymptomatic neurosyphilis by means of routine spinal fluid examination. A negative spinal fluid in a patient with latent syphilis is a practical guaranty against the subsequent development of neurosyphilis (excepting a more or less purely vascular involvement).

The aim of treatment in latent syphilis is to increase the probability of "cure" or "arrest," and to decrease the probability of clinical progression or relapse, over the probable result if no treatment is given. In addition, treatment aims at the control of the potential infectiousness of the latent syphilitic. Of the patients with latent syphilis, 50% of white males, 70% of white females, 80% of negro males, and 90% of negro females had never received any treatment prior to admission. Less than 2% had received anything resembling adequate modern treatment. This, in part, is attributable to the factor of symptomless infection with syphilis, and in part constitutes a serious reflection on current medical practice in the treatment of early syphilis.

An analysis of clinical results as compared to the plan of treatment employed suggests that continuous treatment, especially if it includes large amounts of heavy metal, offers a slightly better chance of satisfactory results than intermittent treatment, and that the intensive plan of arsphenamin administration (daily injections) is productive of a greatly increased incidence of Wassermann fastness. A special analysis of continuous *versus* intermittent treatment indicates that in early latency continuous treatment is as essential as in early syphilis; in late latency this is no longer so imperative and rest periods probably do no harm. An analysis on the basis of the amount of treatment administered suggests that in latent syphilis maximum results are obtained with about 20 injections of arsphenamin combined with large amounts of heavy metal, the latter prolonged over long periods of time.

When results are compared on the basis of the total duration of observation, it appears that the natural tendency of latent syphilis is toward spontaneous "cure," and that this tendency is markedly enhanced by treatment. If the results in the treated patients followed for 10 or more years are contrasted with the hypothetical outcome in untreated patients with latent syphilis, the probability of a satisfactory outcome ("cure" or "arrest") has been increased from 35 to 85%, the percentage of Wassermann positive but clinically quiescent cases reduced from 35 to 7.5%, and the probability of clinical progression or relapse reduced from 20 to 30% to 2 to 5%. This gain is certainly due to treatment. The clinical outcome is better in early than in late latency (satisfactory results 50.8% as compared with 33.7%), and in both groups better when the patient was seronegative on admission (usually as a result of previous though inadequate treatment) than when the blood Wassermann was positive. Distinctly better clinical results were obtained in females who were pregnant during or after treatment than in females never pregnant. The occurrence of suggestive but not diagnostic signs of cardiovascular or central nervous system involvement in patients with latent syphilis does not appear to carry a greatly increased hazard for the patient.

Clinical Progression and Relapse, Wassermann Fastness and Death. Moore further states⁴ that 94 patients of the total 1936 with latent syphilis were observed to develop clinical relapses. The types of relapse observed were: Early infectious relapse in 16; late cutaneous, mucosal, ocular, or osseous lesions in 15; cardiovascular syphilis in 31; neurosyphilis in 30; and visceral (hepatic) involvement in 5. Negroes are much more liable than whites to develop late relapses in skin, mucosa, eye, or bones. Males are much more liable than females to develop early infectious relapse. Of all relapses 72% occurred after 19 or less injections of arsphenamin. Cardiovascular syphilis is the only form of progression or relapse whose incidence is not markedly reduced by the administration of 20 or more injections of arsphenamin. An analysis of early infectious relapse suggests that the plan of treatment for early latency ought to be identical with that for early primary or secondary syphilis, and that the total duration of treatment should be as great.

Approximately 30% of all patients with latent syphilis have irreversibly positive blood Wassermann reactions. The incidence of Wassermann fastness is slightly greater in patients receiving 19 or less injections of arsphenamin (32.6%) than in those receiving 20 or more. It is more common in late than in early latency, in whites than in negroes, and in non-pregnant than in pregnant women. It is suggested that the natural tendency of Wassermann-fast patients is toward the spontaneous development of serologic negativity. Of 26 known deaths among 1936 patients with latent syphilis, only 5 were attributable to syphilitic infection or treatment for it.

The Course of the Blood Wassermann Reaction in Treated Latent Syphilis. Moore and his associates⁵ conclude that the Wassermann response to the first course of arsphenamin in late latent syphilis is much slower than that obtainable in early syphilis; in early latency it is intermediate between the two. The rate of reversal of the blood

Wassermann is in direct relationship to the duration of infection. With the Wassermann technique employed, Wassermann reversal is secured by a 6 to 8 injection course of arsphenamin in 85% of patients with early syphilis, in 34% of those with early latency, and 24% of those with late latency.

The composite Wassermann curves of patients with latent syphilis under prolonged continuous treatment (4 courses of arsphenamin over a period of about a year), as compared with a similar group of patients with early syphilis, indicates that in latency almost all of the serologic response to be expected occurs within the first 4 months of treatment; further treatment has little effect from the serologic standpoint. Composite curves of patients treated continuously are compared with those of a similar group treated intermittently in early syphilis, and in early and late latency. These show that, from the serologic standpoint, continuous treatment in early syphilis is essential, in late latency unnecessary. Early latency occupies an intermediate position.

The existence of a provocative Wassermann in latent syphilis is confirmed. Its character differs from that of the provocative Wassermann in early syphilis, in that its rise is slower and less pronounced but longer sustained.

A Critical Analysis of 157 Cases of Cardiovascular Syphilis. Wile, utilizing material studied in the University of Michigan clinic⁶ consisting preponderantly of males, points out that there were 30 cases of uncomplicated syphilitic aortitis, 19 of aortitis with heart failure, 73 of aortic regurgitation and 35 of aortic aneurysm. The average duration of infection before cardiovascular involvement was approximately 15 to 20 years. The Wassermann reaction was positive in 73% of patients with aortitis and heart failure and in 96% with aortic regurgitation. Spinal fluid examination in 38% of the total group was positive in from one-fourth to one-half of the cases.

Dyspnea was the outstanding symptom in all cases. The physical findings in the cases of uncomplicated syphilitic aortitis were more or less limited to accentuated aortic second sound, increased retro-manubrial dullness, enlargement on percussion and systolic murmur. In aortitis with heart failure, the most frequent physical findings were enlargement on percussion and edema. The Roentgen ray findings showed a positive and presumptive evidence of aortitis in 67% of the uncomplicated syphilitic aortitis group, 73% of the aortic regurgitation group and 90% of the aortic aneurysm group. From 14 to 37% of the cases had received some antisyphilitic treatment prior to the onset of the cardiovascular involvement, but there were practically none which satisfied the present standard of adequate antisyphilitic treatment.

Arsenical Reaction. Cole's⁷ review of the problem of arsenical reactions leads him to the following conclusions. Among a total of 177,360 injections of arsenical salts, the relative frequency of reactions was 15 per 1000, 13 of which were mild and 2 severe. Mild reactions observed, in the order of their frequency, were gastro-intestinal, nitritoid, slight skin eruptions, pruritus, and transient kidney irritability. Severe reactions observed, in the order of their frequency, were icterus,

crustaceous dermatitis, ocular damage, hemorrhagic purpura, and a few instances of aplastic anemia, hepatitis, and encephalitis. In early syphilis the rate for mild reactions was 3 times higher than for severe reactions. Severe reactions, however, showed their highest rate in primary syphilis, followed by a lessened incidence in secondary and latent syphilis. Mild arsenical reactions were noted more than twice as often in females as in males in both colored and white, while severe reactions were seen more frequently in the whites without regard to sex. Mild arsenical reactions were more common in the early years of life, while severe types seemed to increase as the patients got older.

For mild reactions the rate per 1000 injections was practically the same for old arsphenamin and neoarsphenamin, somewhat lower for silverarsphenamin, sulpharsphenamin, and bismarsen. The incidence of severe reactions following sulpharsphenamin was 3.5 per 1000, a higher rate than that for arsphenamin or neoarsphenamin due to the proportionally high incidence of crustaceous dermatitis and purpura hemorrhagica. The rate per 1000 for tryparsamid was also high, 3.7, on account of ocular damage with an incidence of 3.2. Severe reactions from old arsphenamin were no higher than from neoarsphenamin. Reactions of either a mild or severe type occurred with the greatest frequency during the first course of treatment and dropped off gradually with each succeeding course. Approximately 5% of the patients were susceptible to 2 or more arsenicals. Three of every 100 cases reacted to 2 arsenical salts, 10 of every 100 reacted to 3 salts, 15 of every 100 reacted to 4, and in a final highly susceptible group 1 of every 4 patients reacted to as many as 5 different arsenical preparations. The best measure found to prevent reactions was to postpone further arsenical treatment at least a month, preferably 3 to 6 months. Changing the type of arsenical salts was the next best preventive measure, and lowering the dose was the third.

Among the deaths there were 8 cases of hemorrhagic encephalitis, 2 of toxic hepatitis (liver atrophy), 2 of aplastic anemia with purpura hemorrhagica, 1 of agranulocytic angina, and 4 of dermatitis exfoliativa. Two of the cases of encephalitis and 1 of the patients with toxic hepatitis also had dermatitis exfoliativa, thus hemorrhagic encephalitis and dermatitis exfoliativa were the two most frequent complications of arsenical therapy of syphilis resulting in death. The fatal instances of encephalitis and of dermatitis exfoliativa came after only a few doses of an arsenical, and usually in cases of early syphilis. The proportion of fatal accidents was far higher after sulpharsphenamin than after any of the other arsenical preparations.

Cole⁸ has likewise reviewed the problem of syphilis in pregnancy. The conclusions are so numerous and important that space does not permit inclusion in this review. This phase of the coöperative clinical study deserves special study however by all obstetricians.

Standard Treatment Procedure in Early Syphilis. Stokes has summarized the principles underlying the present-day management of early syphilis.⁹ These articles are so replete with pertinent details that they do not lend themselves well to abbreviation and should be read by all physicians who attempt to treat the disease in the most critical stage of its evolution from the standpoint of the individual as well as the public health.

The authors emphasize that the modern system for the treatment of early syphilis must be *continuous*; it must employ an arsphenamin and bismuth, the latter intramuscularly; it must call for not less than 20, and unless special resistiveness is encountered, hardly more than 30 injections of the arsphenamin; and in accordance with the principles generally recognized in the treatment of the disease, the system should call for continued treatment with heavy metal for 1 year after all symptoms and signs of the disease have disappeared. In order to determine this end point, blood tests should be taken at least at the beginning and end of each arsphenamin course and the patient should be warned of the lack of significance of the negative report from the standpoint of the schedule. Weak positives, after a negative has appeared, should be taken as seriously as strong or fully relapsing positives. A spinal fluid examination with Wassermann, cell count, protein estimation, and colloidal gold test should be made before the end of the arsphenamin phase of treatment or the introduction of any rest period (none to be allowed until after the first year). It is understood that such a system can be carried through only with adequate tolerance on the part of the patient, and this tolerance should be conserved in every possible way. If it fails, the case becomes one for consultation. The same system should be employed whether treatment is begun in the seronegative or seropositive primary, or the secondary stage.

All the above articles represent a monographic coöperative effort in syphilology which is a noteworthy achievement in American medicine, and are deserving of critical study by all physicians who attempt to treat syphilis.

V. C. G.

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ORIGINAL ARTICLES.

THE SPLEEN IN HODGKIN'S DISEASE, LYMPHOSARCOMATOSIS
AND LEUKEMIA.*

By PAUL KLEMPERER, M.D.,
PATHOLOGIST, MOUNT SINAI HOSPITAL,
NEW YORK CITY.

(From the Division of Laboratories, Mount Sinai Hospital.)

IN the differential diagnosis of diseases of the hematopoietic system the spleen justly receives a great share of attention. The relative size of the spleen is of comparatively little diagnostic value in the differentiation between lymphadenosis and myelosis, although it is true that the average weight is far greater in the myeloid type of hyperplasia. Individual cases of leukemic or aleukemic lymphadenosis, however, not infrequently present great degrees of splenomegaly. Enlargement is valuable for the differential diagnosis between aleukemic hyperplasia (true pseudoleukemia) and those atypical, more neoplastic proliferations of the lymphatic and myeloid system, such as lymphosarcomatosis, which also run aleukemic courses. The spleen in lymphadenosis, as a rule, presents a diffuse infiltration of hematic cells; for this reason cut surfaces of the organ likewise differ from those found in lymphosarcomatosis. In lymphosarcomatosis, if the spleen is affected, it is mottled by scattered circumscribed nodules up to hazelnut size. These lesions are regarded as hematogenous metastases. Their sharp definition and striking white color differentiate them from the splenic infiltration

* This and the following 4 papers formed part of a round table conference on certain diseases of the hematopoietic system, held at the Memorial Hospital, in connection with its fiftieth anniversary celebration, May 25, 1934. The fifth paper of the symposium, by Dr. Elise S. L'Esperance on "Role of the Tubercle Bacillus in Hodgkin's Disease, Lymphosarcoma and Leukemia," will be published later.

of Hodgkin's disease. The well-known porphyry spleen is often a useful touchstone for the recognition of Hodgkin's disease in the gross, yet it should be remembered that in some cases of the disease the spleen may escape involvement entirely or may even present a diffuse enlargement which is neither macroscopically nor microscopically typical.

The microscopic appearance of the spleen generally conforms to the macroscopic. The detailed histologic characteristics of the different forms are no doubt well known to everyone present today. It is not amiss to mention, however, that the cellular infiltrations of myeloid leukemia may consist of other bone marrow cells as well as myelocytes and their precursors. In rare instances there are large numbers of megakaryocytes and erythroblasts. The differential diagnosis between *lymphatic* and *micromyeloblastic* leukemia may likewise cause difficulty. The clarification of such cases usually depends on detailed cytologic investigations, preferably of splenic spreads. In acute leukemia, especially in infancy, the immaturity of the infiltrating cells may make classification impossible. The topographic distribution of the cells may likewise fail as a criterion, since the Malpighian corpuscles—the chief landmark—are often obliterated. Cases of this sort are best designated *hemocytoblastic* or *stem cell leukemia*.

The classical publications of Drexler, Kundrat, Sternberg, and Reed seemed to have classified the generalized diseases of the hematopoietic mesenchyme for all eternity. But the years have brought increasing numbers of atypical cases, and at the present time even such authoritative pathologists as Mallory and Warthin would abandon the rigid classifications of our predecessors. The unitarian view now demands serious consideration. The clue is possibly in the spleen and I shall, therefore, invite you to consider first the relative positions of lymphadenosis and lymphosarcomatosis.

This question is not a new one. Without discussing in detail the neoplastic aspect of leukemia, it may be sufficient to repeat that recent experiments suggest a close genetic relation between leukemia and lymphosarcomatosis. (For human pathology the term leukosarcomatosis was devised by Sternberg to segregate those cases which manifest a marked aggressive tendency of the cellular proliferation in addition to a leukemic picture. Although this nomenclature might seem to imply a relation of leukemia and lymphosarcomatosis, Sternberg actually emphasized a strict separation of these disease groups. Kundrat, however, had observed the transformation of aleukemic lymphadenosis into lymphosarcomatosis.)

Another link between lymphadenosis and lymphosarcomatosis is supplied by the cases of giant follicular hyperplasia of the lymph nodes and spleen, originally described by Brill, Rosenthal and Baehr.¹ While early phases here resemble aleukemic lymph-

adenosis, necropsy years later presents evidence of tumor formation of lymph nodes and invasion of neighboring structures, precisely as in lymphosarcomatosis.² In only a few cases was the spleen examined during the early hyperplastic phase of the process. The organ was greatly enlarged, the cut surface was dotted with innumerable nodules composed of small and large lymphocytes around the follicular arteries and their ramifications. This appearance differs from the familiar diffuse splenic infiltrations of lymphatic leukemia, yet it is not rare in that dyscrasia (Bezançon,³ Lubarsch, Figs. 136 and 138⁴). It is interesting that 1 of the cases of follicular lymphoblastoma developed a blood picture characteristic of chronic lymphatic leukemia. At necropsy the spleen showed the appearance which I have just described. All of the lymph nodes were found to be enlarged. They were discrete except in the pancreatic region where infiltration of the capsule and adjacent areolar tissue was noted. In the other autopsied cases splenomegaly gradually disappeared before the fatal term of the disease. Microscopic examination, however, showed that the Malpighian corpuscles were large and that considerable cell atypism was still present. In other respects, it may be reiterated, these latter cases conformed to the anatomic picture of lymphosarcomatosis because of conspicuous aggressive tumor formation of the lymph nodes with infiltration of the neighboring organs. These observations suggest that the follicular lymphoblastoma represents a definite link between lymphadenosis and lymphosarcomatosis. In the early stages of its evolution the process is merely hyperplastic, while in the later stages it becomes atypical and aggressive.

In classic lymphosarcomatosis, moreover, 2 cases of a series of 16 showed enlarged Malpighian corpuscles composed of atypical lymphoblasts with hyperchromatic nuclei.

All such experiences point to a close affinity between the *simple hyperplastic* and the *neoplastic* proliferations of the lymphatic system. This is evident even in the spleen, the appearance of which has hitherto constituted one of the chief reasons for strict separation. It is necessary to state, however, that the *generalization* of the cellular proliferation militates against the rigid identification of either lymphadenosis or lymphosarcomatosis with the malignant neoplasms. (Orth's term, *hemoblastosis*, implying unlimited hematic cell proliferation, might serve to encompass lymphadenosis and lymphosarcomatosis in a single domain.)

The coördination of these morbid processes simplifies the comparison with Hodgkin's disease. A number of eminent pathologists include all 3 under a single category, basing this concept largely on microscopic evidence. This tends to undervalue the macroscopic evidence, and I, therefore, dissent from this belief. In my own opinion the evaluation of an individual case is greatly dependent on the gross appearance of the spleen. Whenever the spleen is

involved in Hodgkin's disease the alteration is macroscopically characteristic and can easily be differentiated from the splenic lesions observed in the hemoblastoses. Those splenomegalies of Hodgkin's disease which are not characteristic, such as described by Jona and Torre,⁵ which I have twice been able to verify, may be grossly indistinguishable from the enlargement in the hemoblastoses; but microscopic differentiation is assisted by the absence of hematic cell infiltration. The identification has been proposed not only because of clinical analogies but also because of an alleged transition from one type into the other. This transition is supposedly proved by changes found in repeated biopsies. Such proof loses validity when one recognizes that several lymph nodes removed *simultaneously* may often exhibit wide histologic variation. Moreover, *in a single biopsy* it is not rare to encounter insurmountable difficulties in the differential diagnosis between reticulum cell sarcoma and the monotypic forms of Hodgkin's disease. Such cases are clarified only at necropsy, and the gross appearance of the spleen is sometimes decisive in the final diagnosis. In a previous publication⁶ I have set forth the reasons why I believe that Hodgkin's disease is essentially a granulomatous process. Today I shall only repeat that in both macroscopic and microscopic features the spleen of Hodgkin's disease differs fundamentally from those of the hemoblastoses.

(Finally, I should like to refer briefly to the spleen in the so-called *reticulosis*. (This term refers to those cases in which the entire hematopoietic system is involved by proliferation of large cell forms of reticulo-endothelial origin). The systematized lipoid histiocytoses (Gaucher's and Niemann-Pick's diseases) are related, but because of their chemical characterization are not included. The concept of reticulosis is not yet sharply delimited, and cases of apparently diverse pathogenesis have been included. For this reason the appearance of the spleen has not been found constant, both nodular and diffuse infiltrations having been described. Only a few of the cases have presented a proliferation of cells in reticular arrangement corresponding to the type of embryonal reticular mesenchyme and only such cases should be dignified with the title of reticulosis.

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IS TYPICAL HODGKIN'S DISEASE AN INFECTION OR A NEOPLASM?*

BY E. B. KRUMBHAAR, M.D.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE,
PHILADELPHIA, PA.

THE most important views as to the nature of Hodgkin's disease are that it is either: (1) An infection of unknown nature (lymphogranuloma) (German school, Longcope,† MacCallum, Symmers, etc.); (2) an atypical form of tuberculosis (Sternberg, l'Esperance); (3) a lymphoblastoma (Mallory, Warthin); (4) a megakaryocytoma (Medlar); (5) a disease intermediate between infection and neoplasm (Lubarsch, Levin). The proper nosologic position of Hodgkin's disease is far from being, as some would have it, an almost wholly academic question. The direction of further study, with eventual practical matters of diagnostic and therapeutic importance obviously are largely conditioned by one's attitude to such nosologic aspects.)

Since Hodgkin's description, 102 years ago, of a disease with lesions in the "absorbent glands" (lymph nodes) and spleen that has since come to bear his name, the landmarks as to concepts of the nature of the disease may be roughly outlined as follows: Hodgkin himself paid little attention to its nature, other than to reject the idea of an acute inflammation. In fact, it is generally accepted that of his 7 cases at least 3 represented other diseases of the lymphoid apparatus (tuberculosis, syphilis and leukemia). In 1864, Virchow¹ included Hodgkin's and Wilk's meagerly described group with lymphosarcoma—a nosologic beginning which has over-influenced future developments. One has but to read Virchow's masterly pioneer lecture to realize that this particular statement should carry no weight today in a consideration of the nature of Hodgkin's disease. (After Virchow's and Bennett's² isolation of leukemia in 1845, Cohnheim assembled similar enlargements of lymph nodes without the leukemic blood picture into the group, "pseudoleukemia." Hodgkin's disease, like lymphosarcoma, fell into this group, without concern about its etiology; and it was not until 1893 that Kundrat³ segregated the now familiar lymphosarcoma in a distinctly different sense than the term Hodgkin's disease conveyed.) Desirable at one stage of progress, like "splenic anemia" in another field, Cohnheim's term "pseudoleukemia" seems now to have about reached the limit of its usefulness and be ready for the discard.

* Also presented at the Section of Pathology of the Am. Med Assn., Cleveland, June 11.

† As references to the extensive literature on Hodgkin's disease are easily available in the summaries by Simonds⁵ and Wallhauser,⁶ many are not repeated here.

Toward the turn of the century, two contributions were made that continue to influence two of the chief schools of thought in this problem. In 1898, Sternberg⁴ regarded the condition as a peculiar form of tuberculosis, a view that has steadily found adherents and recently been supported by l'Esperance's¹⁵ production of a Hodgkin-like process with avian tubercle bacilli from Hodgkin's material. Wallhauser⁶ has listed 27 points of possible relationship between Hodgkin's disease and tuberculosis.³

(Sternberg⁷ also began the delineation of a characteristic histologic appearance, which, furthered by the descriptions of Reed,⁸ Andrewes,⁹ Longcope¹⁰ and others, has given at least one firm basis for classification. This picture is so well known that one need only refer to the main features of "endothelioid" cell hyperplasia, with characteristic Sternberg-Reed (and occasionally) Langhans giant cells, frequent eosinophils and other infiltrating cells replacing the normal lymphoid structure, with progressive fibrosis and often varying degrees of necrosis. If, as Warthin, who later became one of the chief advocates of the neoplastic theory, originally suggested,¹¹ "it would appear wisest to limit the pathologic diagnosis of Hodgkin's disease to the chronic inflammatory type of Reed, Longcope, etc., until its etiologic nature is discovered," then much confusion would have been avoided. Unfortunately, however, there has never been agreement on this point, and it must be admitted that many cases clinically diagnosed as Hodgkin's disease fail to give this picture. With biopsy material so easily available, and the increasing use of the biopsy method, it would seem obvious that the histopathologic report, unquestionably the most concise evidence available, should be made a paramount item in the clinical diagnosis, and only those cases diagnosed as Hodgkin's disease that conform to the histopathologic requirements. Insistence on this point—of Hodgkin's disease as a *pathologic* concept—would *ipso facto* eliminate the confusion of including a variety of conditions under the term because they happened to have similar or indistinguishable clinical pictures. Occasional splenic, abdominal and other forms might, to be sure, remain during life or even permanently undiagnosed, but even this is both scientifically and practically preferable to the present loose method of using the term now as a clinical and now as a pathologic diagnosis. In this connection, too, the dangers of such diagnoses as "atypical Hodgkin's disease" must be recognized, if we wish to avoid a morass like that of pseudoleukemia. Substitution of the word "doubtful" would often be as useful and always less confusing.

On this histopathologic basis I have examined the tissues of all fatal cases diagnosed as Hodgkin's disease in our department. Of the 40 so listed, 7 can be rejected as not meeting the histologic requirements (either obviously pure tuberculosis, blastomycosis or without sufficient data). Of the 33 remaining, none revealed a

demonstrated progress from the granulomatous to the sarcomatous picture of Hodgkin's disease—Ewing's Hodgkin's sarcoma. In 3 there was strong probability that the condition was sarcomatous from the beginning or reasonable doubt as to whether Hodgkin's disease or lymphosarcoma in one or other form was under consideration.) If any of the 3 were the latter, however, the evidence for a previous Reed-Longcope histologic picture was never at hand. In the 33 cases there were 22 males, 11 females; the average age was 46, with extremes of 18 and 72 years. Evidence for an associated active tuberculosis was present in 3 cases, but may well have been overlooked in others. There were, of course, others with healed lesions, pleural adhesions or apical scars, but it was not believed that the autopsy records were sufficiently detailed to make an analysis of this item worth while. In 3 cases obviously careful study had excluded tuberculosis, as far as possible, once including bacteriologic and inoculation studies.

In other words, this material lends no support for the primary neoplastic nature of Hodgkin's disease, unimpressive evidence in favor of a causative relationship of tuberculosis and no examples of progress from the granulomatous to the neoplastic type of Hodgkin's lesion.) It brings us definitely back to the probable basis of a granulomatous infection of unknown etiology.

Let us now review the accumulated evidence bearing on the infectious *versus* the neoplastic origin of Hodgkin's disease, granting that it must be regarded as indicative rather than conclusive:

1. *Histologic Picture.* (Whether in lymph node (on which earlier studies were made), spleen, bone marrow or elsewhere, the histologic picture, especially in the early stages (an increase of the "endothelioid" cells of pulp and follicles, together with lymphocytes, eosinophils—first noted by Goldman—neutrophils and plasma cells), is characteristic of chronic inflammation, but would be unique for neoplasm, even a neoplasm of the reticuloendothelial system. The great increase of eosinophils in a considerable number of cases in the tissue and perhaps also in the blood is again a picture unknown in neoplasms but not uncommon in parasitic and other chronic infections, allergy, etc. As the process progresses, the characteristic "Sternberg-Reed giant cell" becomes more prominent, suggestive in different form of such infections as syphilis and tuberculosis, especially as these cells sometimes resemble the Langhans type. Pullinger¹² and Haythorn have emphasized the probable origin of these cells from the reticuloendothelial system, and Foot has pointed out that the reticulum formation suggests that of an inflammatory process. Of course, on the other hand, admixtures of giant cells in sarcoma are not uncommon. The rôle of this cell in Medlar's megakaryocytoma theory will be discussed later. The suggestion, seldom made, that the endothelioid cells are neoplastic is negated for the pathologist by their similarity to cells of accepted inflamma-

tory reactions and the dissimilarity of their pale nuclei and orderly growth to characteristic sarcoma cells. With increasing age of the lesion, fibrosis becomes more and more prominent, some nodes being almost entirely converted into fibrous tissue, with few of the earlier cells remaining—a condition common to many non-neoplastic lesions of lymphoid tissue, but rare in such extreme degree in untreated neoplasms. Even the cell degeneration and areas of necrosis appear to the pathologist's eye more like those of an infection such as tuberculosis or syphilis, than of neoplasm. The general histologic picture, to be sure, sometimes resembles superficially that of sarcoma or even a sclerosing type of carcinoma metastasis, but it also sometimes comes close to that of atypical tuberculosis.

The most important feature in the histologic picture that supports the neoplastic nature of Hodgkin's disease is the neoplastic development late in a certain number of cases of lymphoid tumors of the kind, called by Ewing, Hodgkin's sarcoma. However, as Ewing himself indicates, this picture is only found in a minority of cases. In fact, a critical review of the literature of such cases reduces acceptable cases to a very small number indeed. Such a picture, of course, can easily be reconciled with the infectious theory, by regarding it as a localized neoplastic transformation as a result of the chronic irritation, in the same sense that many other neoplasms are thought to originate. Thus we might say that the characteristic histologic picture of Hodgkin's disease could only be harmonized with the primary neoplasm theory, if one assumed that it was an inflammatory response, of a type not known in connection with any other neoplasms, to an existing neoplasm whose presence in the tissue cannot be demonstrated.

Metastasis. The spread of the process to distant parts, metastasis if you will, is no more indicative of tumor metastasis than of the unknown and hypothetical infectious agent initiating the process in several parts, or transmitting it by blood or lymph. Tuberculosis and various other infections can metastasize or spread throughout the body as well as neoplasms. The tendency to invade, that some have invoked to support the tumor theory, is sometimes less marked than is the tuberculous process in lymph nodes; certainly in Hodgkin's lesions morbid cells are not found in the capsule to the extent that they are in malignancy, and mitoses (except in the Hodgkin sarcoma form) are infrequent.

Fatal Outcome. Exponents of the malignancy theory invoke the invariably fatal outcome as an argument, but we have enough devastating infections, and some that work slowly, to let us accept with equanimity that another, especially when no potent treatment has been devised, might always be fatal. Leprosy was in the same stage a few years ago, while pernicious anemia, due to constitutional defect, was uniformly fatal until Minot's liver treatment was discovered.

Megakaryoblastoma. The latest exponent of a primary neoplastic origin of Hodgkin's disease is Medlar,¹³ who suggests that it is a "megakaryoblastoma," arising from the megakaryocyte of the bone marrow. This was suggested by his observation in experimental tuberculosis (avian and bovine), both of numerous cells resembling the giant cells of Hodgkin's disease, which were taken to be megakaryocytes, and also of a hyperplasia of megakaryocytes in the bone marrow with a wandering-out into the tissues. In a further study of 22 human autopsies and about 100 surgical specimens (but including only 6 bone marrow instances), he found "hyperplasia of the marrow with a marked increase of immature cells which probably are the progenitors of megakaryocytes," with similar picture elsewhere in the body. Adopting the unitarian theory of hematopoiesis, the author suggests that Hodgkin's disease thus becomes closely related to the myeloid leukemias and the erythroblastic dyscrasias. A novel addition to the suggested etiology and nomenclature of Hodgkin's disease (Wallhauser lists 52 proposed names!), and apparently offered chiefly in a provocative way, this hypothesis does not excite one's enthusiasm. Aside from the general limitations on making difficult classifications solely on the basis of morphology, in this case a considerable further assumption is required, namely, that the immature cells in the bone marrow are progenitors of megakaryocytes. Nor do the illustrations furnish impressive support: Granted that the lesions are those of Hodgkin's disease—and I* believe that the bone marrow is more often involved in this disease than has hitherto been appreciated—and granted, of course, that the characteristic giant cell may be found in other tissues, sometimes even in mitosis, both items that are generally acceptable, this by no means indicates that a neoplastic megakaryocyte is necessarily responsible for the lesion. In fact, the very observations that led to elaboration of the theory, namely, the occurrence of similar cells in experimental tuberculosis, are evidence in support of an infectious rather than a neoplastic explanation for the picture found. The prevalent opinion that both endothelioid and giant cells are derived from the reticuloendothelial system has both *a priori* and evidential support.¹⁴ Medlar also suggests that the prominent late fibrosis may be due to organization of excessive fibrin, the formation of which is connected with an increased number of platelets. The assumptions required to support such a view are too numerous to demand more than its notice.

No Demonstrated Etiologic Agent. An important argument that is raised against the infectious theory of Hodgkin's disease is the failure to find an accepted microörganismal cause. It must at once be admitted that the long list of diphtheroid bacteria, spirochetes, amebæ and (most recently) monilia and so on have not been acceptably substantiated.

* AM. J. MED. SCI., 182, 764, 1931.

The most persistent of these claimants is some atypical form of the tubercle bacillus, both because of the well-known frequent association of the two diseases in question (Ewing's apt dictum that tuberculosis follows Hodgkin's disease like a shadow), but also because of suggestive positive evidence that has more than once been produced. Sternberg's frequent finding of tubercle bacilli in Hodgkin-like lesions led him to accept them as the active cause either of the disease itself or at least of a similar subvariety of pseudoleukemia. The latest contribution to this aspect, l'Esperance's¹⁵ recovery of avian tubercle bacilli from Hodgkin's material and experimental production of Hodgkin-like lesions, is too recent to have reached final appraisal. Against her findings must be placed the failure of others to get similar results (but how often has this not been the experience of medical discoveries?) or to benefit patients with serum from inoculated fowls.¹⁶ The vastly preponderating opinion of a whole generation (based mostly on failure to find acid-fast organisms or tuberculous lesions in Hodgkin's material) has been that there is no, or at most a secondary, relation of tuberculosis to Hodgkin's disease.

The most recent development in this field of etiology is the demonstration that ultramicroscopic material (Seitz filter) from Hodgkin's lesions, especially when rendered more potent by refrigerated maceration, can produce characteristic lesions when injected into rabbits and guinea pigs.¹⁷ If the opinion is substantiated that this procedure has diagnostic value, it will not only be a great relief to have a biologic as well as a morphologic attack on biopsy material, but it also should advance our understanding of the disease and perhaps place it definitely in the group of virus diseases. With the known prevalence of latent virus diseases in laboratory animals, however, and their activation by non-specific agents, attribution to this virus of a causative rôle in Hodgkin's disease must be made with utmost caution. Although Fox's¹⁸ small material has thus far been confirmatory, Rhoads and Stewart,¹⁸ in New York, have not been able to reproduce Gordon's result.

Twort's¹⁹ uniformly negative attempts to uncover an infectious agent led him to the pessimistic view, that "one might be dealing with a new growth," but fortunately such councils of despair rarely gain much support.

Immunity. Warthin²⁰ includes among the arguments for neoplasm that no evidence of immunity has been produced. But in the absence of a known specific cause, this objection hardly assumes serious proportions.

A Disease Between Infection and Neoplasm. The suggestion has been made that Hodgkin's disease is unique in being intermediary between infection and neoplasm. Except for the possible occasional sarcomatous transformation of the granuloma (*i. e.*, sarcoma not an integral part of the disease), this idea is both difficult to accept

and without progress value. Concepts of infection and of neoplasm and of transformation from infection to neoplasm are definite and useful, but a hybrid essentially between the two should not be admitted into the present etiologic scheme of disease.

Miscellaneous Evidence. A number of lines of evidence must be regarded as favoring neither infection nor neoplasm. Age, sex, seasonal incidence, geographic distribution, occurrence of the disease in several members of the same family, simultaneous occurrence in twins, and in mother and new-born child,²¹ fever, anemia, reaction to irradiation, general signs and symptoms, duration and similar phenomena may with almost equal justification be invoked to support either the infectious or neoplastic hypothesis. The relapsing type of fever, eosinophilia and impossibility of transmission to animals have led Barron²² to support the parasitic nature of the disease; but no parasite has been incriminated.

Thus, while it is apparent that the nature of Hodgkin's disease remains obscure, the preponderance of evidence favors the infectious theory, with some promising support for its inclusion among the virus diseases. It must be conceded, too, that the stimulus to further progress is greater if it is not included among the malignant neoplasms, at least until compelling evidence is forthcoming. Certainly the growing tendency in this country to relegate it to the already complex and ill-defined group of lymphoblastomata seems ill-advised, both as confusing, against the evidence and inhibiting progress. In the present state of our knowledge of the subject, the term "lymphogranuloma" is also inadvisable. The non-committal designation, "Hodgkin's disease," even though largely based on a picture unknown to the original describer, is to be recommended until a definite etiology has been established. It is a source of satisfaction, then, that the Lymphatic Tumor Registry has seen fit to preserve the independent position of Hodgkin's disease.

Summary. 1. The results of 33 cases of fatal Hodgkin's disease are briefly analyzed.

2. Evidence for the infectious or neoplastic nature of Hodgkin's disease is presented and discussed.

3. Use of the term Hodgkin's disease (rather than lymphogranuloma or lymphoblastoma) and restriction of its use solely on a pathologic (not a clinical) basis is demanded.

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THE DIFFERENTIAL DIAGNOSIS OF AGRANULOCYTIC ANGINA FROM ACUTE LEUKEMIA.

BY HENRY JACKSON, JR., M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

(From the Thorndike Memorial Laboratory Second and Fourth Medical Services [Harvard], Pathological Laboratory, Boston City Hospital, the Department of Medicine, and the Collis P. Huntington Memorial Hospital, Harvard University.)

For reasons that are not clear, the syndrome commonly called agranulocytic angina is now a relatively common one throughout the country. A few years ago the diagnosis was virtually never made, even in the large general hospitals. In the last few years scores of cases have been reported from all parts of the country. The reason for this apparent increase is not clear—it may partly be attributed to more complete and more careful hematologic studies and to better diagnosis; but we may be reasonably certain that the disease has actually increased very considerably. Its etiology and even its pathology are obscure. The condition carries with it a grave prognosis, even with the best of therapy. At the same time a considerable number of these cases recover either spontaneously or following the administration of some more or less specific drug and remain well over a sufficiently long period of time to be regarded as true cures. The condition, however, is easily confused with a far more serious disease—acute leukemia, which is generally conceded to be invariably fatal in a comparatively short period. These facts show the importance of careful differential

diagnoses. From my experience with these two diseases I have drawn certain conclusions which I would like to present briefly.

Let us consider 2 patients. The first is a man, aged 40. His previous health has been good, in fact he has been unusually strong. Three weeks before admission to the hospital he had a sharp chill, an increase of temperature and severe general malaise. Recovery was rapid and complete. Two weeks later a similar episode ensued. Again within 24 hours he seemed as well as ever. Two days before admission to the hospital he began to have malaise, sore throat, chills, generalized abdominal pain and a severe ache in the lower rectum. Prostration was marked. On examination he was found to be mildly delirious. The gums were swollen and ulcerated but not bleeding. The throat was red and parched looking. The temperature was 103° F. There were enlarged and tender lymph nodes in each side of his neck. The heart and lungs showed no abnormalities. The spleen descended two fingers below the ribs on inspiration. The liver was not palpable. In the rectum could be felt a soft, tender mass which did not bleed on palpation. His red count was 4,000,000 per c.mm., the white count 1200 per c.mm. and the platelets slightly increased. The differential count disclosed complete absence of neutrophils, over 90% of the white cells being mature lymphocytes. There were 2% stem cells and the remainder were young monocytes. The red cells showed no abnormalities.

The second case presented a somewhat similar picture. The patient was a man, aged 45. His past history was irrelevant. A week before admission he began to have profuse bleeding from his gums. Fever and sweating was noted from the onset. Malaise was extreme and the patient became rapidly weaker. Three days before admission several large ecchymoses appeared on the outer aspect of his thigh. There had been no preceding trauma. The day before entry he complained of pain in his rectum and passed a small quantity of bright blood. On admission, the physical examination showed him to be extremely pale and sweating profusely. The mucous membranes were pale and slightly cyanotic. The gums were swollen and bleeding profusely. There was some bleeding from his nose. There were palpable and tender lymph nodes in both sides of his neck. The heart and lungs were normal. The spleen was enlarged to the level of the umbilicus. Three large ecchymoses were present on the outer aspect of his right leg. Rectal examination revealed an exquisitely tender, soft, bleeding mass just inside the sphincter. The temperature was 100° F. and the pulse 90. Subsequent examination of the blood showed the white count to be 1000 per c.mm., red count 2,100,000 per c.mm. The platelets were completely absent. The differential count showed 100% stem cells. The red cells were achromic and a rare normoblast was seen.

The first case to my mind is typical of agranulocytic angina; the second a classic example of acute leukemia. There could, I believe, have been no reasonable doubt as to the diagnosis, and the ultimate outcome of the 2 cases proved the correctness of the original diagnosis. The first man is alive and well now, 3 years later; the second man died within a few months, and the bone marrow showed a picture entirely consistent with the diagnosis of acute leukemia.

The differential diagnosis between the two conditions rests largely on the blood picture and to a far less extent, in my opinion, on the signs and symptoms. In acute leukemia there is usually a great reduction of platelets, very frequently they are completely absent. This is not the case with agranulocytic angina, for in this disease the platelets are usually normal, often increased and very rarely diminished. In acute leukemia, anemia is usually marked and progressive and is of the macrocytic type. Anemia in agranulocytic angina is rarely, if ever, of any moment and when present is usually to be attributed to associated but unrelated causes and is of the microcytic type. In acute leukemia, especially in adults, the blood smear shows a considerable number of very immature cells, often virtually all the white blood cells are stem cells and it is only in the most atypical cases that young forms are few in number. A few stem cells may be found in the blood of patients suffering from agranulocytic angina; any very considerable number, however, indicates the probability of leukemia, and the more there are the greater the probability. A level is reached, perhaps 20%, which if more than temporary almost certainly means leukemia. During convalescence from agranulocytic angina there may be, and in fact usually is, a temporary outpouring of myelocytes, but this stage is soon passed and clinical improvement is evident coincidentally.

Agranulocytic angina is very rare in childhood. I have seen no case under 12 years of age and very few under 20. Acute leukemia is not uncommon in childhood, occurs most frequently in early adult life and is rare in old age. Agranulocytic angina is seen in a fair percentage of the cases in the aged.

Leukemic patients with temperatures of 102° to 104° F. may seem comparatively well. This is rarely the case with agranulocytic angina. In this latter disease such temperatures are almost invariably accompanied by marked prostration and toxicity. In agranulocytic angina the fever is either steady or more commonly fluctuates within certain rather definite limits. In acute leukemia the temperature curve is often an extremely variable one.

It should be emphasized that the total white count is of no vital importance in the diagnosis of leukemia. Leukemia is still leukemia whether the white count be 50 or 50,000 per c.mm. The character of the white cells and the pathologic changes in the bone

marrow determine the diagnosis. In the last analysis sternal bone marrow puncture may have to be resorted to as a diagnostic aid.

Our thesis so far seems simple and yet I am convinced that it is not. The first case to which I referred recovered and after a somewhat stormy convalescence has remained perfectly well for over 3 years, but so also did our second case recover temporarily in a manner not at all dissimilar from that of the first and with hematologic changes which were to a certain extent parallel. After 5 days, during which time he had been treated with pentnucleotid, there was a sudden drop in temperature and gradually, over a period of weeks, his blood returned to normal in every respect. The lymph nodes disappeared. The spleen and liver receded, the gums cleared and the patient returned to his usual work, with neither clinical nor hematologic signs of leukemia. He remained perfectly well for over 5 months, but then was suddenly seized with excruciating headache. A week before this episode his blood had been entirely normal. On admission, however, the white count was found to be 20,000 per c.mm., with 80% stem cells, and he was dead in 10 days. The bone marrow showed the characteristic picture of acute leukemia.

Acute leukemia is, of course, subject to temporary remissions, but they are rare and usually of very short duration and almost invariably either the clinical or the hematologic picture shows unmistakable signs of the continued presence of the disease. In the case under consideration, such was not the case. It must, therefore, remain an open question as to the exact nature of his first attack.

The more I see of cases of extreme leukopenia the more certain I become that the differential diagnosis between the various pathologic entities which underlie this syndrome may be well nigh impossible.

A woman, aged 60, whose past health had been good, was taken with severe right lower quadrant pain, chills and high fever. Her white count was found to be 1000 per c.mm., with 100% normal lymphocytes. The platelets and red count were normal. In 2 days she was dead and a retrocecal abscess was found at autopsy. To my mind the diagnosis lay between primary agranulocytic angina with secondary sepsis and primary sepsis with consequent leukopenia. An examination of her bone marrow revealed the fact that it was studded with miliary tubercles and the active myeloid elements had completely disappeared.

A man, aged 50, had had repeated attacks of extreme leukopenia with intervening intervals of perfect health. In all respects, so far as I am able to judge, the case was typical of the relapsing type of agranulocytic angina. However, gradually anemia developed, hemorrhages appeared, the intermittent extreme leukopenia became

constant and death ensued. The bone marrow again revealed miliary tuberculosis with aleukogenesis.

A man, aged 68, was admitted to the hospital with a classic picture of chronic myelogenous leukemia. The white count was 175,000 per c.mm. The spleen descended to the umbilicus. The liver was grossly enlarged. The patient received moderate Roentgen ray therapy without apparent benefit. Two months later the spleen had disappeared, the white count was 1000 per c.mm., the differential showed the vast majority of the cells to be normal lymphocytes. The platelets were normal. Had the patient been seen for the first time at this stage of his disease, he might well have been considered to have agranulocytic angina. He died shortly afterward, and at autopsy the bone marrow showed virtually complete absence of myeloid cells and great activity on the part of early red cells. The liver and spleen showed no gross or microscopic changes.

We must, I believe, recognize that the most classic leukemia can become not only aleukemic but also aplastic. We all recognize that similar bone-marrow changes may be reflected by varied blood pictures. It must also be remembered that very similar blood pictures may be associated with the most varied pathologic changes in the bone marrow and other organs.

In any consideration of the etiology, therapy or diagnosis of any condition it is wise, I believe, first to ask whether the condition under consideration be a distinct entity, recognizable as such by biopsy or postmortem examination. If it is not, I believe our efforts should be aimed toward the clarification of this angle of the subject. We have recently reviewed very carefully the bone marrow on some 20 cases which showed extreme leukopenia without significant involvement of the red cells. The pathologic pictures found varied so much that, frankly, we were unable to give many of them any specific diagnosis. Some we believe to be true and classic agranulocytic angina, others with clinical pictures, not very dissimilar, have shown postmortem many of the earmarks of leukemia. Still others reveal what, for lack of a better term, we refer to as aleukogenesis, no representatives of the myeloid series being present. No doubt the criteria set forth in the beginning of this paper will suffice in many instances to draw a distinction between agranulocytic angina and acute leukemia; but it is my belief that until this former disease, or rather syndrome, is placed upon a more sure pathologic foundation it will be difficult, if not impossible, to distinguish the less fatal types of leukopenia from the probably always fatal acute leukemia.

FIVE-YEAR SURVIVAL IN HODGKIN'S DISEASE.

By LLOYD F. CRAVER, M.D.,
ATTENDING PHYSICIAN, MEMORIAL HOSPITAL,
NEW YORK CITY.

(From the Memorial Hospital for the Treatment of Cancer and Allied Diseases.)

As Hodgkin's disease is uniformly regarded as incurable, no one attempts to speak of 5-year cures, as in cancer. As was emphasized by Stone, of this hospital, 10 years ago, the best results in treating Hodgkin's disease are obtained if one accepts its incurability as a fact and proceeds accordingly with therapeutic measures designed to secure the best palliation for the longest possible time. Such an attitude is not inconsistent, however, with the use, at times, of rather heavy irradiation. Yet it does restrain one from the needless overburdening of the patient with such massive doses as are employed to good purpose, for instance, in the Coutard technique of treatment of hypopharyngeal cancer.

The average length of survival of patients with Hodgkin's disease from the time the symptoms appear is 3 years or less. It is well known that some cases run a much more rapid course, while a few stand out as having run a much longer course. Stone showed that of 164 patients there was complete restoration of health after treatment, either with or without complete disappearance of objective evidence of disease in 32 per cent. In these cases the duration of life subsequent to treatment averaged 35 months, as compared with an average of only 16 months for the whole group.

Among the more important reports concerning length of survival in Hodgkin's disease after irradiation are the following:

Burnam reported 28% of 147 cases showing a survival of 5 years or more following Roentgen therapy, with 14 surviving 8 years or more. These results are so exceptionally good that the question arises as to what proportion of cases in this series did not have the diagnosis confirmed by biopsy. Schreiner and Mattick, in 1924, reported 46 cases, of which 31 had been treated by high voltage Roentgen rays or radium pack. Their average survival was 2 years and 7 months. (It is not clear whether this figure represents survival following irradiation or recognized onset.)

Voorhoeve, in 1926, reported 19 cases. Of 11 which had been treated according to plan, 7 were dead, with an average survival of $2\frac{1}{2}$ years following irradiation, and 4 were living with an average survival of 3 years.

Gilbert and Babaiantz, in 1931, reported that of 25 cases treated since 1922, there were 15, all verified by biopsy, that had received treatment according to plan. These had the remarkable average survival following Roentgen therapy of 4 years and 9 months.

Five patients died after an average survival of $2\frac{1}{4}$ years. Four died on an average of $4\frac{1}{2}$ years following Roentgen therapy. It is noteworthy that 6 of the 15 patients were living an average of over $7\frac{1}{4}$ years. Gilbert and Sluys take pains to point out, however, that since 1928 they have received 27 new cases and that they can see already that in this group they are not going to obtain as long an average survival as in the cases reported. They, therefore, advise great caution in judging individual results.

McAlpin and Golden, in 1933, reported 42 cases with positive biopsies. Five patients were still living at the time of their report, 2 for over 10 years. Of the 32 patients who had been followed throughout their course, 6 had survived over five years. In the deceased patients, however, the average duration of the disease was only 2 years and 8 months.

Analysis of Memorial Hospital Figures. A recent survey of the case records of this hospital gives the following figures. From 1918 to June 1, 1929, 125 cases of Hodgkin's disease verified by biopsy were treated. Because of the fact that for several years we pursued the fad of treating cases of supposed lymphosarcoma and Hodgkin's disease largely without benefit of biopsy, we have in our records a considerable number of additional cases which, because of their clinical course, we have good reason to believe were Hodgkin's disease; 185 cases, in fact. A third group of 53 more doubtful cases is not included. This makes a total of 310 cases either proven by biopsy or believed to be proven by clinical course, treated between 1918 and June 1, 1929.

Of these 310 cases, 32 (10.3%) showed a survival following irradiation of 5 years or over. Of the proven cases, numbering 125, 15 (12%) showed a survival of over 5 years.

Living are 16 patients over 5 years since they came, in 9 of these the diagnosis being proven by biopsy. These 9 living patients have survived an average of 7.4 years since treatment and have an average total duration of life since onset of symptoms of 9.5 years.

Our service in the treatment of Hodgkin's disease has increased considerably in recent years. We now have in the current file, records of 77 cases, proven by biopsy, and 17 cases, without biopsy, but almost certainly Hodgkin's disease. A number of doubtful cases is excluded.

As an attempt to find reasons for the marked extremes of duration, of course we have made for comparative purposes a brief analysis of a group in which there was a total survival of 1 year or less following onset of symptoms and a survival of 6 months or less following irradiation. In this group were 22 cases, of which 9 were proven by biopsy and 13 were presumably Hodgkin's disease.

As to age of patients, we find that the 5-year survivors averaged 34 years of age and varied between extremes of 6.5 and 67 years, while those surviving 6 months or less averaged 44.3 years and

varied from 7.5 to 67 years. Thus we find that there is practically no difference between these two groups with respect to age limits, and we also find the rather surprising fact that the patients with the shorter courses were, on the average, 10 years older.

The male-female ratio was 11 to 10 in the 5-year group; 14 to 8 in the 6-month group.

As to average duration of the disease before treatment, we find in the group of 5-year survivors that the symptoms had existed previously for from 1.5 months to 8 years, the average being 1.4 years; while in the 6-month cases, symptoms had been present previously for from 1.5 months to nearly 1 year, the average being 4.4 months.

What reasons can we find in our survey of these two contrasting groups of cases for the great difference in length of course? The simplest statement, but one which does not explain the difference, is that the disease was more virulent or malignant in the one group. An analysis of the presenting complaints in the two groups indicates that in the cases of short survival there was evidence of generalization in 16 of the 22, while in the cases with long survival uncomplicated lymphadenopathy with few or no general symptoms was the rule. We have seen that, contrary to the usual impression, the cases with the longer survival were not in the older age groups, but in the younger, averaging 34 years as against 44.3 years.

Examination allows us to say with safety that variations in histology of nodes as removed at biopsy do not account for the different duration of course. Many of the cases pursuing the longer courses have shown highly cellular types of Hodgkin's disease, approaching sarcoma.

As to location of disease we have the distinct impression that localization in one area, preferably the upper cervical region, combined with early thorough treatment, perhaps with early surgical removal followed promptly by thorough irradiation, offers the most favorable prognosis.

A nearly normal blood count seems to be favorable, while leukocytosis with or without polynucleosis, or leukopenia, are unfavorable.

Fever and marked pruritus, and pronounced splenomegaly seem to be unfavorable prognostic signs.

A tendency to gain greatly in weight soon after irradiation seems to be a good indication.

Yet 1 of our patients now living, 8 years since treatment was begun, had advanced pulmonary tuberculosis with cavity formation and positive sputum when admitted.

As to treatment, the long-surviving cases on the whole seem to have fared with only a moderate amount of irradiation; but this statement should be qualified, I think, by stating that, as a rule, in the cases with long survival the early lesions were treated fairly vigorously and persistently.

I should like to add a statement of impression concerning our present technique which consists mainly of divided doses of high voltage Roentgen therapy, as contrasted with the technique of 5 and 10 years ago, when for the most part single massive doses of low voltage Roentgen rays were used. Our regressions now seem better with less immediate discomfort, but are we not seeing more marked leukopenia and more cases of later debility and leukopenia than in former years? I wonder whether some cases might not do better with the older technique.

Summary. Of 310 cases of Hodgkin's disease, 125 proved by biopsy, 10.3% showed a survival following irradiation of 5 years or over—of the proven cases, 16.8%.

Five-year survivors averaged 10 years younger (34 years of age) than a group that had survived 6 months or less, though extremes of age were the same in the two groups.

The difference in survival of the two groups is apparently due to differences in virulence of the disease. This, however, showed no correlation with the histologic appearance of nodes removed at biopsy. Favorable features were localization in one area, combined with early thorough treatment, absence of leukocytosis or leukopenia, gain in weight after irradiation. Fever, marked pruritus and splenomegaly were apparently unfavorable signs.

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IRRADIATION IN LYMPHOSARCOMA, HODGKIN'S DISEASE AND LEUKEMIA.

(A STATISTICAL ANALYSIS.)

BY T. LEUCUTIA, M.D.,
HARPER HOSPITAL, DETROIT, MICH.

NEARLY 15 years have now elapsed since the introduction of deep Roentgen ray therapy, which has produced such pronounced changes in our concepts regarding the value of irradiation in general and of the curative results in particular. It, therefore, appears proper that, at a meeting to commemorate the fiftieth anniversary of one of the leading institutes for the treatment of cancer and allied diseases, we pass in statistical review all that has been accomplished in this domain, therefrom certain conclusions concerning standardization of rational therapeutic procedure may

be derived. Especially is this true of some affections of the lymphatic and hematopoietic systems, such as lymphosarcoma, Hodgkin's disease and leukemia, where radiation therapy, because of the extremely high radiosensitivity of the elements comprising those lesions, played a great rôle from its very incipency.

This review of reports from the literature and of personal observations is concerned with the status which radiation therapy now occupies in the treatment of these conditions. There will be little, if any, new contribution, for the subject is already well covered in all its phases by a wealth of material; but the numerical tabulation of results from distant parts of the world may help to endorse certain more or less universally preferred methods and to harmonize various views concerning the optimum therapeutic effect which may be expected. To this aim, attention will be directed to the following main points: (1) Increase of expected duration of life in the average case; percentage of 5- and 10-year survival with eventual final cure in the individual cases; (2) method of treatment which appears more generally used leading to the optimum effect; and (3) prognostic evaluation during the course of the disease and treatment.

(a) *Lymphosarcoma.* The paucity of the statistical material concerning irradiation of lymphosarcoma is indeed surprising. This is chiefly due no doubt to the lack of knowledge as to what really constitutes lymphosarcoma and in the rather vague precision as to its classification. It seems that the majority of investigators still prefer to consider the condition as a small round cell sarcoma and thus to place it in the rather large group of general sarcoma, without further subdivision or classification. On the other hand, the very close resemblance which exists between this condition and other disorders affecting the lymphoid tissue, such as pseudoleukemia, aleukemia, Hodgkin's disease and even lymphatic leukemia, has induced not a few students of the problem to include them all under the general heading of lymphoblastoma or malignant lymphoma. To take one example of this latter group: Minot and Isaacs,²¹ who on the basis of a rather large number of cases (477) arrived at some very definite conclusions concerning certain points which are of interest to us, state that the average life duration of lymphoblastoma is 2.76 years and that about 10% of both the irradiated and non-irradiated had the disease for 6 or more years. From this they think that radiation therapy, although of great value in producing symptomatic improvement, does not influence importantly the life duration of the group as a whole. Obviously it is very difficult, if not impossible, to obtain comparative data either by including lymphosarcoma in the general group of sarcoma or by placing it under the comprehensive heading of lymphoblastoma. Desjardins and Ford,⁹ well realizing this difficulty, published, in 1923, a first series of 55 cases of lymphosarcoma to determine the life expectancy from the onset of symptoms to death, when no sys-

tematic treatment was given and, in 1926, a second series of 126 cases to ascertain the prolongation of life when radiation therapy was applied. The average duration of life was found to be in the first series $2\frac{1}{2}$ years and in the second $2\frac{1}{3}$ years, indicating that radium and Roentgen ray treatment does not seem to prolong life to a notable degree. The percentage of those who survived longer than 5 years was 10 in the first series and 6 in the second, the longest life duration being 25 years. These results agree well with those of Minot and Isaacs.

TABLE 1.—STATISTICAL ANALYSIS OF RESULTS IN LYMPHOSARCOMA
(The group of lymphoblastoma of Minot and Isaacs is included for purposes of comparison.)

Author.	Period.	Type of lesion.	Cases.	Irradiation technique.			Results.					
				Quality.	Dose.	Extent.	Un-traced.	Alive.	Lived.		Died.	Average survival since onset, yrs.
									5 yrs.	10 yrs.		
Minot and Isaacs, ²¹ 1926	1913-1925 1901-1925	All lymphoblastoma except lym. leukemia	477	No irradiation			..	76	60	16	163	2.45
				Various irradiation							238	2.88
Desjardins and Ford, ⁹ 1923	1915-1920	All lymphosarcoma	102	Without systematic treatment			26	9	6	..	67	2.45
Desjardins, ¹⁰ 1926	1920-1923	All lymphosarcoma	126	140 Kv. 200 Kv.	Large doses	Fairly general	32	25	7	2	69	2.33
Rosenthal, Harris and Kean, ²³ 1931	1918-1931	Follic. lymphosarcoma	10	200 Kv.	Fract. 200 r.	All reg. involved	..	4	4	1	6	4.33
Evans and Leucutia, ¹¹ 1934	1922-1930	All lymphosarcoma	31	200 Kv.	Large doses	Generalized	1	6	10*	4	24	3.33†

* Four died later.

† The average life duration since treatment was 2.1 years.

A tabulation of 31 cases of lymphosarcoma treated from 1922 to 1930 at Harper Hospital shows, however, that systematic irradiation leads to a distinct improvement in results. In our series, 30% lived 5 years or longer, 15% 10 years or longer (for some of the 5-year survivals the 10-year period is not up yet). For those who died, the average duration of life was $3\frac{1}{2}$ years after the onset of symptoms and 2 years and 1 month after the beginning of irradiation. Still better results were reported by Rosenthal, Harris and Kean²⁸ for 10 cases of follicular lymphoblastoma, a more benign variety than other types of lymphosarcoma. In their series, 4 patients are alive from 3 to 12 years, and in the 6 who died the average life duration from the onset of symptoms was $4\frac{1}{3}$ years.

Although the material gathered in this group is not very large, and certainly not as comprehensive as in the groups of Hodgkin's disease and leukemia, we may venture the following statement concerning the value of irradiation in lymphosarcoma:

1. Thorough radiation therapy increases the expectation of life in all forms of lymphosarcoma from $2\frac{1}{2}$ to $3\frac{1}{2}$ years and leads to cure in at least 10% to 15% of the cases. If a subdivision into reticulum cell sarcoma, lymphocytoma and follicular lymphoblastoma is made, the improvement in results shows an ascendancy in the order named. Adding to this the often-observed "spectacular" symptomatic improvement, the largest tumors melting away like snow within the period of a few days, radiation therapy must be considered as the method *par excellence* in the treatment of lymphosarcoma.

2. It is essential that irradiation be carried out with penetrating rays (200 kv., $\frac{1}{2}$ to 1 mm. Cu or Zn as filter), large doses (90% to 100% SUD per field) and wide extension to as much as possible of the lymphatic system, the entire abdomen and the mediastinum being included in the series of exposures, regardless of whether the disease is localized or generalized. It is not unusual by this procedure to have 16 to 20 large portals covered with full or nearly full erythema doses within a period of 2 or 3 weeks, the total amount of radiation absorbed by the body being indeed a considerable one. A severe depletion of the blood with all its sequelæ follows shortly after the completion of the series and, therefore, a very careful management of the patient with administration of blood stimulants and roborants is necessary for several months. The irradiation is repeated in 8 to 10 weeks over the areas of the manifest lesions, which by this time have all disappeared, with a dose of about 70% SUD; and eventually for a third series in another 10 to 12 weeks with a dose of 50% SUD. Since lymphosarcoma, by reason of the lymphatic extension, remains localized to the lymphatic system and a few abdominal organs, such as the intestinal mucosa, serous membranes, spleen and liver, for a longer time, the above procedure leads in a certain percentage of cases, as shown in the statistical analysis, to a complete eradication of the disease. In such instances, no resumption of the irradiation appears necessary after the series is once completed, patients remaining free of recurrences for long periods or becoming cured. This, as we shall see later, is contrary to what occurs in Hodgkin's disease or leukemia. In case there is only temporary regression or the dissemination of the disease continues at a more or less rapid pace, irradiation acquires a purely palliative value and is directed accordingly.

3. The prognosis of lymphosarcoma is governed apart from the radiosensitivity gradation into the three forms (the reticulum cell sarcoma, lymphocytoma and follicular lymphoblastoma) by the extent of involvement at the time of the treatment and especially by the rapidity of growth of the tumor in the period preliminary to treatment. Lesions localized for a longer period to one single lymphatic region, as a rule, are more apt to result in final cure than widely disseminated rapidly growing processes, although in a few

instances we have experienced a complete disappearance of the lymphosarcoma with more than 10-year survival in very generalized forms. Progressive anemia, gradually developing cachexia, onset of fever, etc., usually render prognosis unfavorable.

(b) *Hodgkin's Disease*. In contradistinction to lymphosarcoma, Hodgkin's disease formed a favored topic for statistical study to a rather impressive number of investigators, so that in Table 2 we were able to collect the final results of 14 leading institutions from different parts of the world, based on some 805 cases. As is noted, there is a very close agreement between the various sources, the rationale of the following general conclusions being quite apparent:

1. Radiation therapy, if carried out systematically, in addition to the fact that it leads to great symptomatic improvement, increases the duration of life in the average case of Hodgkin's disease from 2 to about $3\frac{1}{2}$ years, produces a 5-year survival in 15% to 33% of cases, a 10-year survival in 8% of cases and finally leads in certain instances to a symptom-free period long enough beyond the 10-year limit that it may be considered a cure. If the acute cases as well as those which, because of the very far advanced stage, could not be properly treated, are eliminated or set in a group apart, as practised by Voorhoeve,³¹ Gilbert, Babaianitz and Sluys,¹⁴ Hummel¹⁷ and others, the good effect of the irradiation becomes still more apparent. In view of the fact that no other method can equal these results at the present time, radiation therapy must be considered as the treatment of choice.

2. As a general rule, Roentgen ray therapy with penetrating rays (160 to 200 kv., $\frac{1}{2}$ to 1 mm. Cu or Zn as filter) is preferred, although some favorable results are reported also with radium packs which, however, must possess a rather marked intensity. The so-called medium Roentgen rays (120 to 130 kv. with light Al filter) are now practically discarded or reserved for the occasional irradiation of the spleen. The dosage is guided by the general condition of the patient and the severity of the lesion. If the condition is good and the lesion localized, larger doses up to a full erythema dose may be attempted, but if the condition of the patient indicates systemic invasion (fever, pruritus, modification of the blood formula, cachexia, etc.) and the manifest lesions are fairly generalized, the fractionated protracted method will lead to best results. Daily seances of 10% to 30% SUD are given spread over a period of several weeks until all disease foci are covered, a total dose of 50% to 90% SUD being administered per focus. The massive irradiation with large single doses including all lymphatic areas, whether diseased or not, as heralded in the early period of deep Roentgen ray therapy and as successfully practised for lymphosarcoma, has brought only disappointment in the treatment of Hodgkin's disease. It has, therefore, gradually given way in every place where it was used to the more moderate procedures, as

TABLE 2.—ANALYSIS OF RESULTS IN HODGKIN'S DISEASE.

Author.	Period.	Cases.	Irradiation technique.			Results.								
			Quality.	Dose.	Extent.	Untr.	Alive.	Aver. life duration, yrs.		Lived.	Died.	Aver. survival, yrs.		
								Since trtm.	Since onset.			5 yrs.	10 yrs.	Since trtm.
Desjardins and Ford, ⁹ 1923	1915-1920	135	Without systematic treatment			43	10	7	..	82	..	2.55
Desjardins, ¹⁰ 1926	1920-1923	57	140 Kv. 200 Kv. 1 mm. Cu	Large doses	Generalized	10	11	6	2	36	..	3.15
Chaoul and Lange, ⁶ 1923	1923	12	70% SUD; foc. fract. of 10% 70% SUD		Only manifest lesions	..	1	1	2.5	3.0
Schreiner and Mattick, ²⁹ 1924	1924	46	140 Kv., $\frac{1}{2}$ Cu 200 Kv., $\frac{1}{2}$ Cu	70% SUD; foc. fract.	2.55
Voorhoeve, ³¹ 1925	1915-1925	I:11 II: 8	Radium pack 160 Kv., $\frac{1}{2}$ Zn or 200 Kv., $\frac{1}{2}$ Zn	70% SUD; foc. fract. 50% SUD; foc. fract.	Manifest lesions	..	4 2	3.0 0.25	4.4 1.25	7 6	2.6 1.7	3.8 2.3
Brugman, ⁴ 1926	1913-1925	20	...	25% SUD; foc. fract.	Manifest lesions	8	1	3.5	11	2.5	
Burnam, ⁵ 1926	1913-1925	173	Radium pack	25% SUD; foc. fract.	Manifest lesions	13	28	5.15 4.6	4.25 6.25	9	4	110	2.9	4.25
Dautwitz, ⁸ 1927	1925-1926	56	Radium pack	Small doses	Manifest lesions	6	6	1	44	..	3.0
Billich, ³ 1930	1920-1930	31	180 Kv., $\frac{1}{2}$ Zn	Sm. fract. 20% SUD foc.	Manifest lesions	2-3
O'Brien, ²⁵ 1931	1919-1928	19	140 Kv., $\frac{1}{2}$ Cu	Small fract.	Manifest lesions	19	..	3.9
Hummel, ¹ 1932	1920-1928	I:52 II: 4	...	70-100% SUD; later fract.	Manifest lesions	..	10	5.3	6.2	2	1	42	1.9	3.4
Goia, ¹⁵ 1932	1920-1932	63	180 Kv., $\frac{1}{2}$ Zn or Cu	Fract. 150-400r p. field	Manifest lesions	..	17	4.25	5.33	6	1	46	0.2 2.25	1.3 3.2
McAlpin and Golden, ¹⁹ 1933	1922-1932	42	Med. volt., 3 Al; 200 Kv., $\frac{1}{2}$ Cu	$\frac{1}{2}$ -3 SUD	Manifest lesions	5	5	..	5.8	..	2	32	..	2.66
Gilbert, Babaianz, Sluys, ¹⁴ 1933	1922-1928	I:15 II:10	Semi-penetr. 200 Kv., 1 Cu	Fract. 170r Foc. 400r	General; later only manifest lesions	..	6	7.25	..	5	1	9 10	3.5 1.6	
Evans and Leucutia, ¹¹ 1934	1922-1930	46	200 Kv., 1 Cu	70-90% SUD; later fract.	Manifest lesions	..	10	10*	3	36	2.1	3.1

* Five died later.

The subdivision of Voorhoeve, Hummel and Gilbert, Babaianz and Sluys indicates: I, Those cases which received rational treatment and, II, those in which treatment had to remain incomplete because of subsequent complications.

indicated above, only the actually diseased areas being exposed. Following the completion of the first series, the patient is kept under strict surveillance, and as soon as there is evidence of a new focus or of a recurrence, the treatment is resumed. It is generally found that irradiation often must extend over a period of years, many of the 5- and even 10-year survivals being kept alive only by this continuous resumption of the irradiation. If in the advanced stages of the disease, the extension manifests itself only by general symptoms (fever, pruritus, anemia, cachexia, etc.), irradiation of the entire trunk with large fields or teleroentgen therapy will bring about further temporary improvement and relief of symptoms. Here the administration of adjuvants (arsenic, blood stimulants), opotherapy, climacteric therapy, etc., will likewise prove of benefit.

3. If one attempts a prognostic evaluation of a certain case of Hodgkin's disease during the course of the radiation therapy, it may be said that the prognosis is more favorable in the localized form, especially if the lesion remained confined for a longer period to one single group of glands or to one organ. In the generalized form it is more favorable in those cases which run no fever and have a normal blood formula and, finally, in all instances in which there is a prompt regression of the tumefactions following irradiation with long periods of remission. According to Goia,¹⁵ who made a very detailed study of this subject, the prognosis is unfavorable in case of combination with active tuberculosis, involvement of the retroperitoneal glands, elevated and continuous temperature, hyperleukocytosis, exudative pleural or peritoneal effusion, hyperneutrophilia, neutropenia associated with leukocytosis, hypereosinophilia and a rapid recurrence of the tumefactions following radiation therapy.

(c) *Leukemia*. In estimating the precise value of irradiation in leukemia, it appears advisable to separate the acute from the chronic form. Especially is this true of the lymphatic type, where the ratio of the acute to the chronic form may be as high as 1 to 1 or even higher. Since radiation therapy is without even as much as symptomatic effect in the acute cases, the disease continuing its progression toward the fatal end at a rapid pace, their inclusion in the general statistics of leukemia serves only to confuse the issue in the chronic form. To take one example, Cooke,⁷ from a study of 50 cases of acute lymphatic leukemia, found that more than one-half lived 3 months or less from the onset; one-third, 3 to 6 months; and only one-eighth from 6 to 9 months, none having survived the 9-month period. This is also the experience at this hospital following the systemic irradiation of 21 cases of acute lymphatic leukemia. On the other hand, Minot and Isaacs,²² from a study of 30 cases of chronic lymphatic leukemia, without irradiation, estimated the average duration of life from the onset of the disease

in this form as being $3\frac{1}{3}$ years. By combining the two varieties, without specifying their ratio of incidence, obviously one may obtain an average life duration which varies from 1 to 3 years. This point is emphasized in order to furnish an explanation for some of the apparent discrepancies in the statistics of those investigators who, as shown in Table 3, made no distinction between the

TABLE 3.—ANALYSIS OF RESULTS IN LYMPHATIC LEUKEMIA.

Author.	Period.	Type.	Cases.	Irradiation technique.			Results.					
							Untr.	Alive.	Lived.		Died.	Average survival, yrs., since onset.
				Quality.	Dose.	Extent.			5 yrs.	10 yrs.		
Minot and Isaacs, ²² 1924	-1924	Acute	I:42	No irradiation			42	0.3
			II:15	Var. irradiation			15	0.3
		Chronic	I:48	No irradiation			18	30	3.33
			II:50	Var. irradiation			50	3.53
Béclère and Béclère, ² 1913	1904- 1913	Both	12	Benoist 9°	Small	Spleen Lymph nodes	1	..	12	
Schreiner and Mattick, ³⁰ 1924	-1924	Both	16	90 Kv., 4 Al 200 Kv., $\frac{1}{2}$ Cu Radium pack	Fract.	Spleen Lymph nodes General	16	
Fricke, ¹² 1928	1915- 1928	55	Radium pack	1	2.75*
Nyström, ²⁴ 1931	-1931	Both	33	160 Kv., $\frac{1}{2}$ Cu	$\frac{3}{5}$ SUD twice wkly.	Chest, back, abdomen	1.2
McAlpin, Golden, Edsall, ²⁰ 1931	1920- 1930	23	135 Kv., 3 Al 200 Kv., $\frac{1}{2}$ Cu	$\frac{3}{4}$ SUD wkly. $\frac{1}{8}$ SUD wkly.	Sprfel. lymph nodes; deep lymph nodes	2	5	1	..	16	1.5
Arendt and Gloor, ¹ 1932	1921- 1931	26	170 Kv., $\frac{1}{2}$ Cu Zn	10-40% SUD 40% SUD; also AS	Spleen Lymph nodes	6	2	20	2.2
Finzi, ¹² 1932	1920- 1927	Both	16	140 Kv., 5 Al 180 Kv., $\frac{1}{2}$ Cu	80% SUD 100r daily	Spleen Lymph nodes	1	1.5
Cooke, ⁷ 1933	1917- 1932	Acute	50	Var. irradiation and transfusion			50	0.3-0.9
Evans, Leucutia, ¹¹ 1934	1922- 1930	Acute	21	140 Kv., 4 Al	50% SUD	Spleen Lymph nodes	1	21	0.4*
		Chronic	13	200 Kv., 1 Cu	30% SUD						12	4.33

* Fricke's cases had an average survival since treatment of 0.95 year; Evans and Leucutia's of 2.5 years.

two forms. The final impression is that irradiation not only does not lead to a prolongation of life, but produces a shortening of life as compared to the values of Minot and Isaacs.²² There is still another point worthy of consideration: in the statistics of Minot and Isaacs,²² 1.4 years was taken in the chronic forms of both the lymphatic and myelogenous leukemia as the average period which has elapsed between the onset of the disease and the establishment of the first diagnosis. Since it cannot be said that patients are referred for irradiation any sooner, it would be perfectly proper to add the same figure to the final values of those Roentgen thera-

peutists who calculated the average period of survival of their patients from the time of the institution of the radiation therapy. With these corrections, we then find a rather close agreement between the various statistics as indicated in Tables 3 and 4.

TABLE 4.—ANALYSIS OF RESULTS IN MYELOGENOUS LEUKEMIA.

Author.	Period.	Cases.	Irradiation technique.			Results.					
						Untr.	Alive.	Lived.		Died.	Average survival since onset, yrs.
			Quality.	Dose.	Extent.			5 yrs.	10 yrs.		
Minot, Buckman, Isaacs, ²³ 1924	-1924	88	No irradiation			36	..	18	3		3.04
		78	Var. irradiation, chiefly radium								3.5
Béclère and Béclère, ² 1913	1904-1913	93	Benoist 9°	4H fract.	Spleen	93	
Klewitz and Schuster, ¹⁸ 1922	1912-1922	26	Spleen	26	2.5
Schreiner and Mattick, ²⁰ 1924	-1924	9	90 Kv., 4 Al 200 Kv., 1 Cu Radium pack	...	Spleen	9	2.25
Fricke, ¹³ 1928	1915-1928	102	Radium pack	3.0*
Rikl, ²⁷ 1930	1920-1930	31	160 Kv., $\frac{1}{2}$ Zn	50% SUD fract.	Spleen	31	1-4
Hoffmann and Craver, ¹⁶ 1931	1918-1930	75	Radium pack 150 Kv., 4 Al	Small	Spleen	4	71	3.36
McAlpin, Golden, Edsall, ²⁰ 1931	1920-1930	24	200 Kv., $\frac{1}{2}$ Cu	$\frac{1}{2}$ SUD wkly.	Spleen	1	5	18	3.0
Nyström, ²⁴ 1931	-1931	54	160 Kv., $\frac{1}{2}$ Cu	$\frac{3}{5}$ SUD, 3-5 wkly.	Spleen Long bones	2.9
Radajevic, ²⁶ 1932	1927-1932	18	Med. volt., 5 Al Deep 1 Cu	40% SUD 10% SUD	Spleen	3.9
Finzi, ¹² 1932	1920-1927	38	140 Kv., 5 Al 180 Kv., $\frac{1}{2}$ Cu	50% SUD 100r	Spleen Long bones Chest	1.95
Arendt and Gloor, ¹ 1932	1921-1931	39	170 Kv. $\frac{1}{2}$ Cu, Zn	10-40% SUD Fract. AS	Spleen	4.1
Evans and Leucutia, 1934	1922-1930	18	140 Kv. 4 mm. Al	50% SUD fract.	Spleen, occ. long bones	18	3.3*

* Fricke's cases had an average survival since treatment of 1.5 years; Evans and Leucutia's of 2.1 years.

It may be said, from a study of these statistics, including 420 cases of lymphatic and 683 cases of myelogenous leukemia, that:

1. Radiation therapy increases the expectation of life in chronic lymphatic and myelogenous leukemia very little, perhaps with about $\frac{1}{3}$ to $\frac{1}{4}$ of the usual duration without treatment. Several authors are of the opinion that the results are somewhat better in the myelogenous group than in the lymphatic group, but this is not at all apparent if a careful separation of the acute from the chronic cases is made in the lymphatic group. In exceptional

instances (about 1% of the total) patients had a symptom-free life for a rather long period, the longest case in the lymphatic group having survived for 16 years and in the myelogenous group for 16.5 years. Most of these cases, however, have shown an exceedingly chronic nature from the beginning and they did not come to treatment until in the later stages of the disease, when the survival already exceeded the average period of life expectation. Thus if, on the basis of the above statistics, it cannot be said that radiation therapy leads to a cure even in individual cases of leukemia, and if life is prolonged but little beyond the expected duration in the average case, the question arises whether irradiation has a *raison d'être* in the treatment of leukemias or whether one may be content to produce palliation by other non-radiologic methods. A brief observation of the radiation effect should give the correct answer. In nearly every instance, the severe cases not excepted, a prompt and definite response appears shortly after the first few seances of irradiation. The patients are rapidly relieved of their distressing symptoms, start to gain gradually in weight and strength and within a few months are able to resume their work. From this moment on, with the aid of periodic check-up examinations of the blood formula as a guide, the good control of the symptoms can be continued by small series of irradiation given from time to time. It is said that the patient's working efficiency is increased at least 60% throughout the entire course of the disease as a result of the radiation therapy. Whether or not one accepts this as a proven fact, there can be no doubt about the great comfort which is brought about in the great majority of the average cases, so that here, too, we may affirm unhesitatingly that radiation therapy forms the best method of treatment to be followed.

2. There is virtual chaos concerning the technique of irradiation recommended. However, in view of the facts that palliation is all that can be produced and that some effect may be expected from every radiation, no matter under what circumstances and over which part of the body administered, this is not of great importance. Indeed, we see good results claimed from the medium penetrating rays (120 to 130 kv.) with larger doses (50% to 70% SUD) as well as from the harder rays (200 kv.) with smaller fractionated doses (10% to 40% SUD) and from the radium packs; whether the irradiation is made over the spleen, lymphatic system (especially in lymphatic leukemia), long bones (especially in myelogenous leukemia), great vessels of the chest, bones of the thorax, kidneys, entire trunk or even the entire body in the form of teletherapy. From a study of the statistics, it appears safe and perhaps best to pursue the following course: (a) Lymphatic leukemia—the spleen is irradiated with either half erythema doses of medium penetrating or with smaller doses of harder Roentgen rays and the enlarged lymph nodes are treated simultaneously with the

harder rays by making use of the protracted fractionated method which is spaced so as to conform with the changes in the blood formula; (b) myelogenous leukemia—the spleen alone is treated by using half erythema doses of the medium penetrating or smaller doses of the harder rays. The series which usually extends over 2 or 3 months is repeated at shorter or longer intervals depending on the blood formula, and only if no further response is obtained from the exposure of this organ is irradiation extended to the long bones or to the entire body in the form of teleroentgen therapy.

3. The aim of the radiation therapy being to bring about a symptomatic relief and improvement in the general condition of the patient rather than the eradication of the leukemia as a disease, it is unnecessary, even harmful, to try to reduce the white cell count to normal or below normal. If the state of the patient is good and the white cell count is in the neighborhood of 10,000 to 30,000, the irradiation may be temporarily discontinued. Future treatment is then guided by the activity of the leukemia, controlled by periodic blood examinations and a strict surveillance of the general condition of the patient. As soon as there is recurrence of the splenic enlargement or of the tumefaction of the lymph nodes, an increase in the relative or total white cell count of the blood, excessive rise in the number of immature cells and, finally, deterioration in the physical state of the patient, the irradiation is resumed. The anemia, which, as a rule, complicates the later stages of every leukemic, is treated by accessory methods, such as blood transfusions and arsenic, liver extract and ventriculin.

Summary and Conclusions. The present study is based on an analysis of 2425 cases collected from the literature and of 129 cases personally observed. A rather close harmony was found in the different groups collected from leading institutions of various parts of the world and it may be said that irradiation forms the method of choice in all three types of lesions analyzed.

(a) In lymphosarcoma, the 5-year survival amounts to 30% and the 10-year survival or cure to at least 10% to 15%. In the remaining the expectation of life is increased from $2\frac{1}{2}$ to $3\frac{1}{2}$ years. The immediate results often are so prompt and decisive that they may be called "spectacular."

(b) In Hodgkin's disease, the 5-year survival reaches 15% to 33%, but the cases in the great majority remain carriers of the disease, necessitating frequent resumption of the irradiation. A 10-year survival or cure occurs in 8% of the cases or less. In those who died within the first 5 years, the average expectancy of life was increased from 2 to $3\frac{1}{2}$ years. The symptomatic improvement is nearly always marked but not so spectacular as in lymphosarcoma.

(c) No cure is believed to occur in leukemia as a result of the irradiation. The prolongation of the average life duration is

likewise rather insignificant, perhaps with $\frac{1}{3}$ to $\frac{1}{4}$ of the natural expectancy, which is considered to be about $3\frac{1}{2}$ years in the chronic forms of both the lymphatic and the myelogenous type. The symptomatic improvement, however, is remarkable and it is believed that the efficiency of the patient is increased at least 60% throughout the major part of the duration of the disease. In the acute forms of leukemia not even a temporary improvement is observed.

The results of teleroentgen therapy which was started a few years ago are not included in this article, but it is believed that they will not materially influence the above data. Likewise little improvement in the results is expected from the introduction of the Roentgen ray therapy with voltages above 200 kv., except perhaps in certain well-selected cases of localized lymphosarcoma where a higher penetration is needed.

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THE SYNDROME OF ACUTE AGRANULOCYTOSIS AND ITS OCCURRENCE AS A COMPLICATION OF KALA-AZAR.

By LILY S. ZIA, M.D.,

ASSISTANT IN MEDICINE,

AND

CLAUDE E. FORKNER, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, PEIPING UNION MEDICAL COLLEGE,
PEIPING, CHINA.

(From the Department of Medicine, Peiping Union Medical College.)

AGRANULOCYTOSIS and malignant or idiopathic neutropenia are terms which have been used interchangeably to designate a relatively rare type of severe leukopenia which is chiefly characterized by an absence of, or a very marked decrease in the relative number of polymorphonuclear granulocytes in the blood. This condition is not to be confused with simple leukopenia, a common state accompanying many diseases such as pernicious anemia, malaria, typhoid fever, and others. In these latter diseases there occurs frequently both an absolute and a relative decrease of polymorphonuclear leukocytes, but this decrease is not marked and is of significance as a diagnostic rather than as a therapeutic indicator.

Leukopenia of a chronic type and of a moderately severe grade with leukocyte counts of from 1500 to 5000 cells per c.mm. and with granulocytes of from 20% to 60% is the rule in kala-azar. Acute agranulocytosis, on the other hand, has not been reported as a complication of the disease.

During the 8-month period from October, 1932, to June, 1933, there came under our observation 26 consecutive patients who were proved to have kala-azar. Of these, 4 exhibited agranulocytosis as a complication of the disease. Because of the close similarity of these attacks of acute agranulocytosis to those of idiopathic agranulocytic angina and because of the therapeutic problems involved we believe it is pertinent to report these cases in some detail.

Case Reports. CASE 1.—W. H. T. (No. 40207), a male college student, aged 20, was admitted to the general medical service of the hospital on May 4, 1933, because of fever of 2 weeks' duration. Onset was gradual. Fever was accompanied by chilly sensations and general malaise. Slight epistaxis was noticed on the first day. Past and family histories were irrelevant, except that 1 of patient's siblings had had attacks of the schizophrenic type.

Physical examination on admission showed few positive findings. The skin and mucous membranes were pale. The liver was barely palpable. The spleen was 15 cm. below the costal margin. Aside from a few dental fillings, the rest of the physical examination was not important.

Laboratory findings on admission were as follows: Urine, normal.

Stool, normal except for the presence of ova of ascaris. Blood, red blood cells, 4.44 millions per c.mm., with 9.4 gm. hemoglobin; the white blood cells were 1350 per c.mm., with 48% granulocytes.

The diagnosis of kala-azar was proved by recovery of Leishman-Donovan bodies from the spleen and from the marrow of the sternum. Neostibosan,* 2.75 gm., divided into 11 doses, was given intravenously. The first 4 injec-

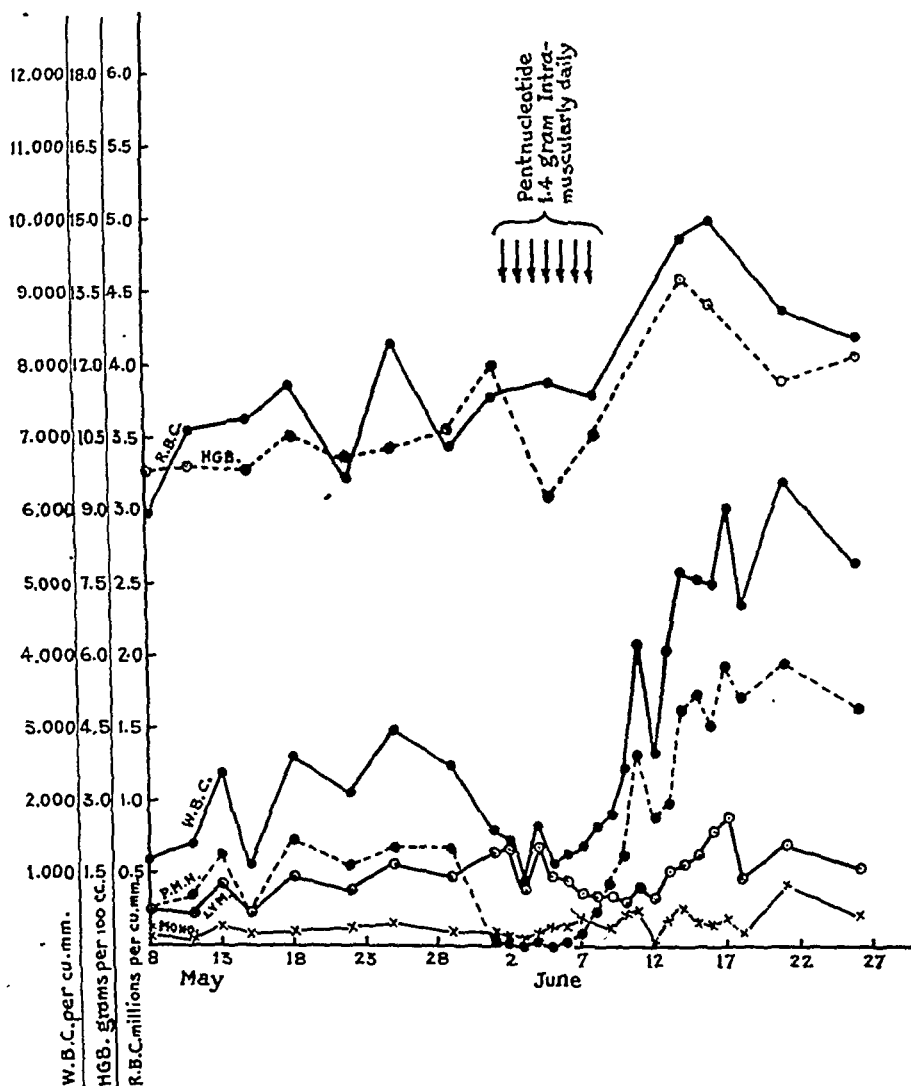


FIG. 1.—Case 1. Showing the fluctuations in blood cells and a period of acute agranulocytosis.

tions were given every day. The subsequent doses were administered every second day. During the first 3 weeks of treatment, patient showed noticeable clinical improvement, although the anemia and leukopenia persisted (Figs. 1 and 2). The polymorphonuclear neutrophils varied from

* Neostibosan-p-amino-phenyl stibinate of diethylamin, containing antimony in the pentavalent form.

44 to 56%. On May 29, 3 weeks after the beginning of the treatment, 1 day before the last injection was due and after 10 days of normal body temperature, patient had diarrhea without blood or mucus in the stool. Only a few white blood cells were seen when the stool was examined under the microscope. Blood studies done on this day showed no appreciable

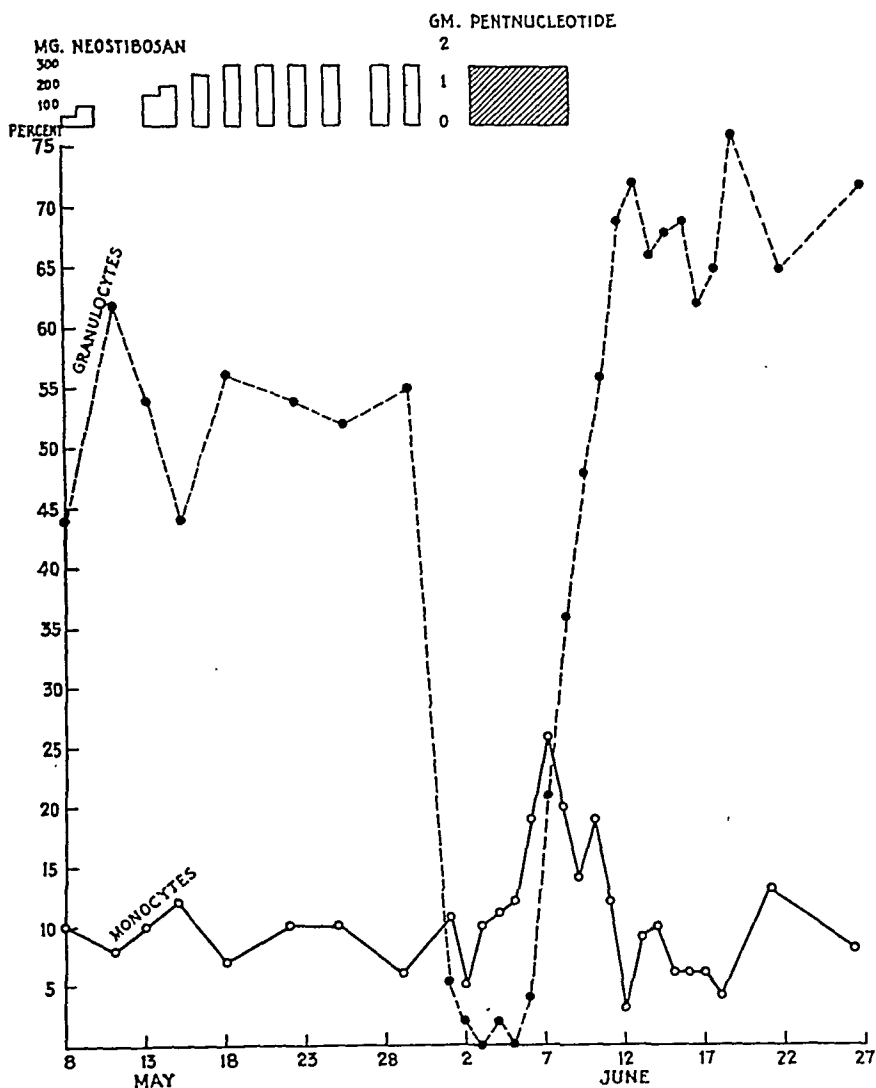


FIG. 2.—Case 1. Showing the dramatic changes in relative values of granulocytes and monocytes.

changes (red blood cells, 3.44 millions; hemoglobin, 10.6 gm.; white blood cells, 2450, with 55% granulocytes). Diarrhea continued and on May 31 there was fresh blood in the stool. On careful questioning the patient stated that he felt more ill and that he experienced a sense of fatigue and exhaustion. The next day a drop in the total count of the granulocytes was observed (total white blood cell count, 1550; granulocytes, 5.3%).

On June 2, 4 days after the onset of the diarrhea, and the second day after the rapid decrease of granulocytes was discovered, the body temperature was raised to 38.6° C. (total white blood cell count, 1450; granulocytes, 1%).

During the next few days the granulocytes completely disappeared from the peripheral blood and the patient was critically ill with sustained high body temperature (Figs 1 and 2). A few small shallow ulcers were seen on the buccal mucous membrane on the fourth day of the agranulocytosis and there was enlargement of the regional lymph nodes. The diarrhea, however, subsided. As soon as the acute agranulocytosis was discovered, antimony was withheld and pentnucleotide,* 0.7 gm., was given intramuscularly twice daily for 7 successive days. At about the height of fever, the fifth day of the agranulocytosis, the patient became mentally disoriented, and a diagnosis of toxic psychosis was made. With the increase of the granulocytes in the peripheral blood, which was evident from the fifth day of treatment with pentnucleotide, patient's body temperature came down and all signs of infection of the mucous membrane disappeared. Mental condition was also improved.

Blood cultures, on May 14, June 6 and 9, were all sterile. Stool cultures for pathogenic organisms were negative on 6 occasions, while 3 examinations for protozoa and ova after the onset of the diarrhea were negative. Wassermann and Kahn blood reactions were negative.

Summary. A patient with early kala-azar treated with Neostibosan developed agranulocytosis near the end of the course of treatment. No evidence of sepsis. The disease picture was complicated by the development of a psychosis. Treatment with pentnucleotide given. Improvement in the blood and clinical pictures occurred.

CASE 2.—H. C. F. (No. 37879), a male college student, aged 28, was admitted to the general medical service of this hospital on October 25, 1932, with history and physical and laboratory findings of kala-azar. The characteristic history dated back to 9 months, with insidious onset and gastro-intestinal disturbances.

On admission, the red blood cells were 2.35 millions; hemoglobin, 7.05; and 1600 leukocytes (61% were granulocytes) (Figs. 3 and 4).

The patient was treated with Neostibosan intravenously. A total of 3.05 gm., divided into 13 injections, was given during a period of 3 weeks. The body temperature gradually came down to and stayed at normal levels until November 21, after the patient had received the 13th injection, when it rose to 39° C. During the whole course of the disease the patient stated repeatedly that he felt very tired. Prior to the rise in body temperature this feeling of exhaustion was intensified. The patient complained of sore throat, but examination of the throat showed only some congestion. For the next 6 days there was agranulocytosis (Figs. 3 and 4), and patient was critically ill, with body temperature remaining above 39° C. No ulcers were seen in the mouth. The submaxillary lymph nodes were enlarged and tender. On November 24 there was a furuncle on the bridge of the nose and another on the lobe of the left ear. On November 25, 5 loose stools were passed, whereas until this time the patient had been constipated. Stools were black, contained mucus, many white blood cells and a few red blood cells. Patient was transfused twice, on November 26 and 29, with 400 cc. of whole blood each time. With the improvement in the blood picture, the superficial infections gradually healed and had disappeared on November 29. The next day the body temperature became

* Pentnucleotide—a mixture of sodium salts of pentose nucleotide prepared from the ribonucleic acid of yeast.

normal. The recovery was uneventful, although the patient had a protracted convalescence.

Summary. A patient with clear-cut kala-azar, treated with Neostibosan, developed transient agranulocytosis at about the end of treatment. Had superficial infection of the skin and enlargement

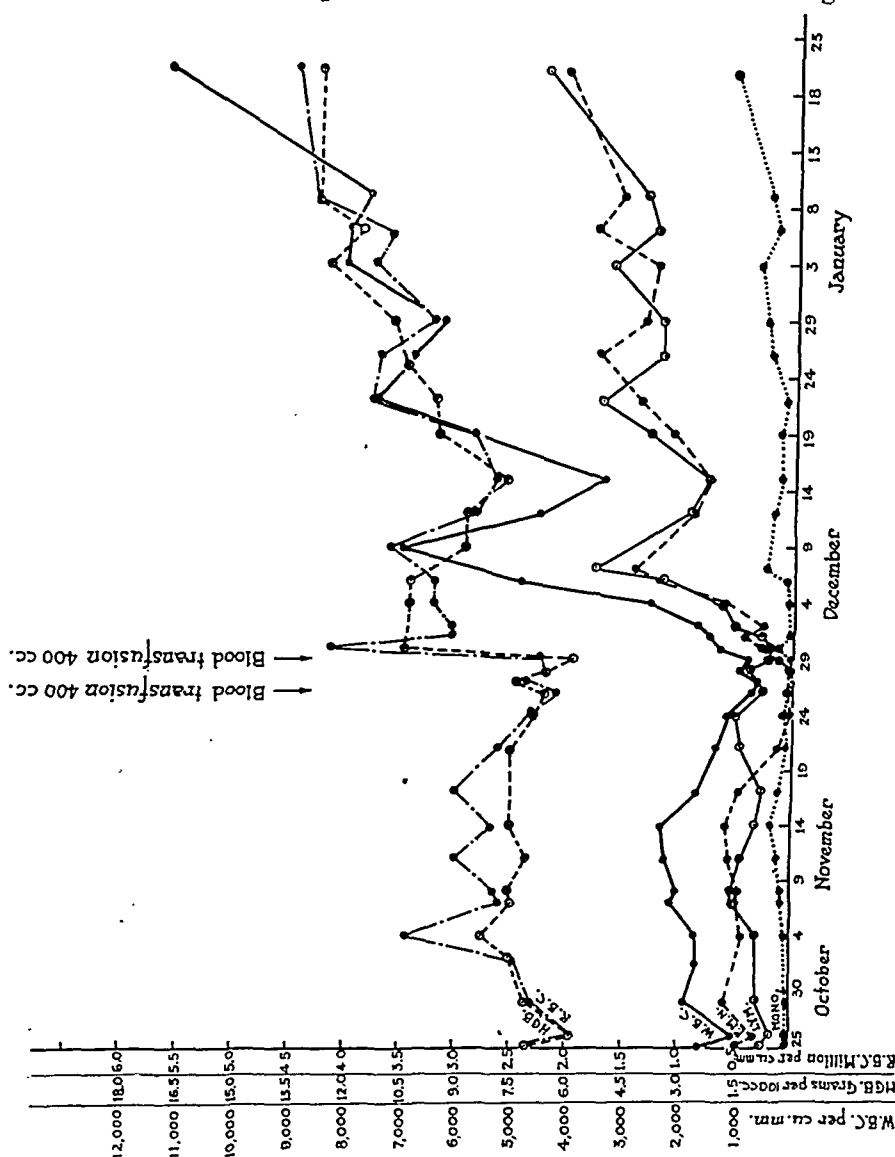


Fig. 3.—Case 2. Showing transient agranulocytosis during the course of studies on the blood cells.

of the cervical lymph nodes without evidence of sepsis. Two blood cultures and 5 stool cultures were negative. Transfused with whole blood. Recovery.

Comment on Cases 1 and 2. These 2 cases present certain features in common. On admission both patients had moderate leukopenia.

Both were treated with the same compound of antimony, Neostibosan. In both, a state of agranulocytosis was discovered 1 day before the last injection was due. Both were progressing satisfactorily when the agranulocytosis developed. The granulocytes of the blood were totally absent in Case 1, a few were present in

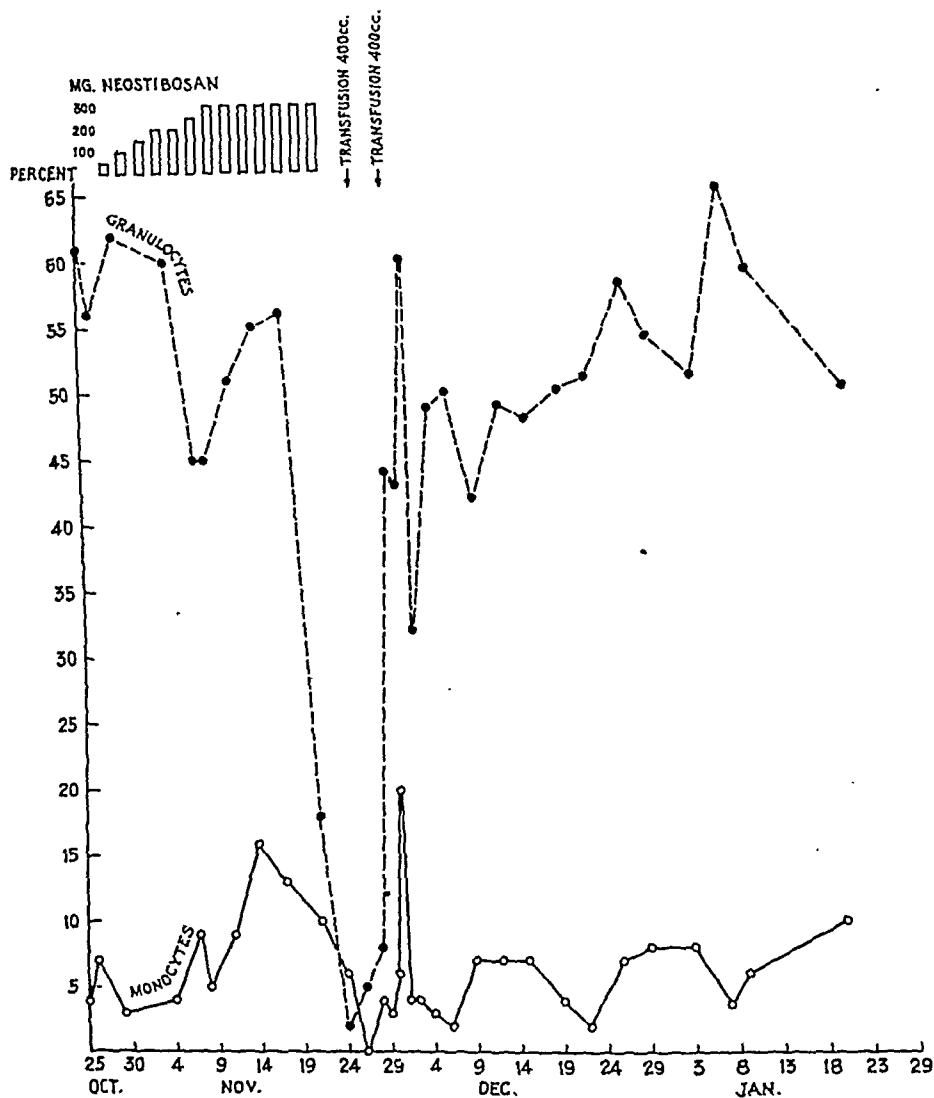


FIG. 4.—Case 2. Showing abrupt changes in relative numbers of granulocytes and monocytes.

Case 2. In neither was there any evidence of sepsis. Both patients had slight superficial infection with enlargement of the cervical lymph nodes, coming on after the onset of agranulocytosis. Both had some intestinal symptoms and signs, simple diarrhea in Case 2 and suggestive dysentery in Case 1. Pentnucleotide was given in Case 1 while blood transfusion was resorted to in Case 2. Both

patients had increases in the total white blood cell counts and percentages of granulocytes after the 5th day of the agranulocytosis. Both recovered from the transient agranulocytosis.

CASE 3.—C. M. M. (No. 38709), a female baby, aged 11 months, was admitted to the pediatric service of this hospital because of high fever of 2 weeks' duration. Past and family histories were irrelevant. On admission the important physical findings were: (1) Moderately enlarged and

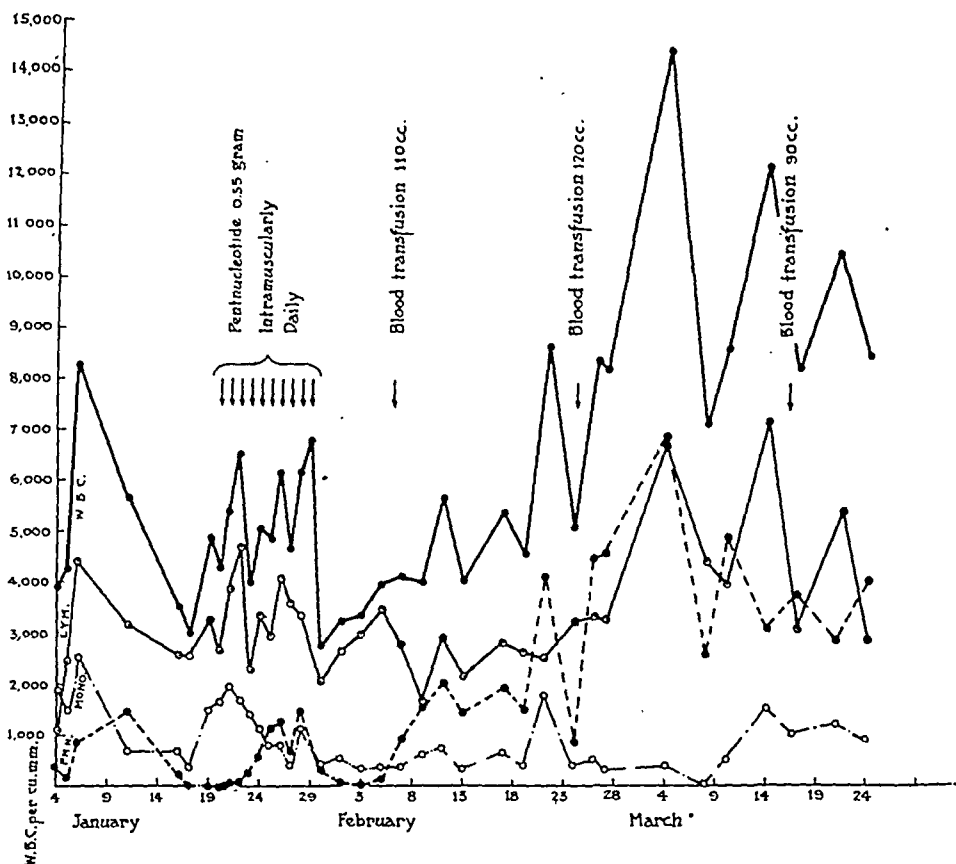


FIG. 5.—Case 3. Showing recurrent agranulocytosis. Only the total white blood cell and differential counts are given. The hemoglobin values and the red blood cell counts did not show any significant change except as results of blood transfusions.

injected tonsils; (2) palpable but non-tender cervical lymph nodes; (3) a small ulcer at the tip of the tongue; and (4) liver 3 cm. below the costal margin in the right midclavicular line. The spleen was not palpable.

The blood showed moderately severe anemia (hemoglobin, 6.9 gm.) and moderate leukopenia (total white blood cell count, 3900). Differential white blood cell count showed only 9% neutrophils, while the monocytes were as high as 48%.

The patient's course in the hospital was as follows:

January 3 to 16, there was no change in the general condition; had a low-grade fever.

January 17 to 21, corresponding to the period of agranulocytosis (Figs. 5

and 6), there were high body temperature, reaching 40.6° C., swollen gums and enlarged and tender cervical lymph nodes.

January 22 to 31, improvement in blood and clinical pictures, but low-grade fever persisted.

February 1 to 6, agranulocytosis and high fever recurred. Smear of material obtained by puncture of liver showed a few Leishman-Donovan bodies. Spleen became palpable. There was again enlargement of the cervical lymph nodes. There was seen in the throat a white membrane,

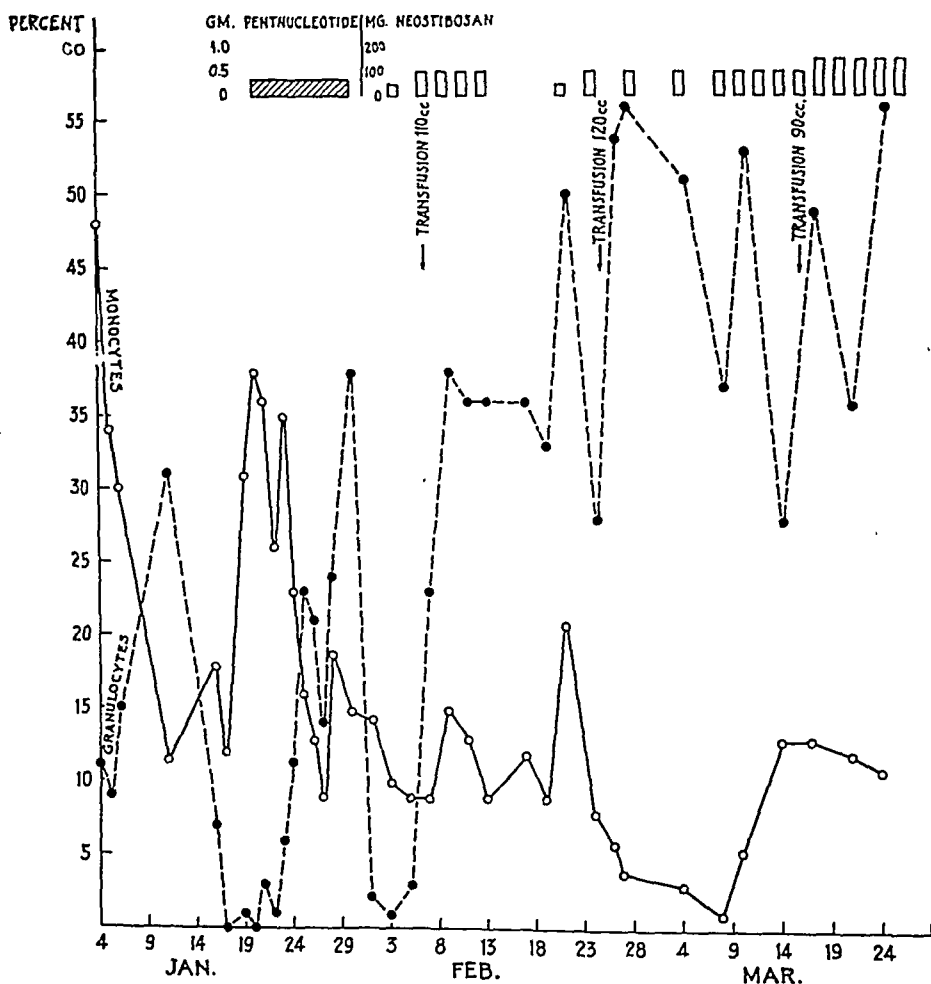


FIG. 6.—Case 3. Showing marked fluctuations in the percentage values of granulocytes and monocytes.

not unlike that found in diphtheria. Smear from the membrane showed *B. diphtheriae*, and patient was given 20,000 units of antitoxin intramuscularly.

February 9 to 12, membrane in the throat showed no progress.

February 13 to 17, fever and a rash appeared, which were diagnosed as serum sickness.

February 20, lesions in throat healed.

Blood transfusions in small amounts were given 3 times, with a total of 320 cc. of citrated blood. Treatment with Neostibosan was started on

February 3. Three blood cultures done at different intervals were all negative. Patient was discharged from the hospital on March 29, well, after receiving a total of 2.05 gm. of Neostibosan.

Summary. An infant suffering from early kala-azar and without any treatment showed cyclic changes in the number of the granulocytes in the peripheral blood. These fluctuations were accompanied by appearance and disappearance of ulceration of the mucous membrane and rise and fall of the body temperature. Such changes were not observed after the institution of treatment for kala-azar. No evidence of sepsis. Recovery.

Comment on Case 3. The spontaneous cyclic changes in the number of the granulocytes in the peripheral blood is of interest. During the period of observation the granulocytes were absent on 2 occasions during 1 month. With the agranulocytosis there were elevation of the body temperature and ulceration in the mouth or throat with enlargement of the regional lymph nodes. The exact time relationship between the two was not clear-cut since daily blood counts were not done. Attention is called to the fact that the total white blood cell count was never below 2500. On one occasion it was 4850 when the percentage of granulocytes was zero. This agranulocytosis was no longer observed after treatment with antimony was started. On several occasions after the beginning of recovery there occurred leukocytosis.

CASE 4.—L. W. C. (No. 37685), a boy, aged $9\frac{1}{2}$, was admitted to the pediatric service of this hospital, on October 10, 1932, because of irregular fever, distention and a mass in the left upper quadrant of the abdomen for 7 months, general anasarca for more than 1 month and dyspnea, palpitation of heart and slight productive cough for 1 week. No mention was made of bleeding from any source. Past and family histories were not important.

On admission, patient was found to be very ill, with marked subcutaneous edema and ascites. There was light bleeding from the gums, with beginning noma. The bases of the lungs were compressed and the heart was displaced upward. The spleen was 14 cm. and liver 2 cm. below the costal margin in the midclavicular lines.

The laboratory findings on admission were as follows: Urine and stool showed no important abnormal changes. Blood: red blood cells, 2.66 millions; hemoglobin, 7.1 gm. per 100 cc. of blood; white blood cells, 800. Differential white blood cell count showed complete absence of granulocytes. These counts were confirmed repeatedly.

Smear of the material obtained from puncture of the spleen 2 days after admission showed numerous Leishman-Donovan bodies. Two days later the patient suddenly died of respiratory failure.

Necropsy confirmed the clinical findings and the diagnosis of kala-azar. Because of the agranulocytosis, the blood-forming organs were of special interest. The spleen was tremendously enlarged (1060 gm.) and very soft in consistency. Its surface was smooth and bluish-gray in color. There were several deep notches along the medial margin. On section the surface was slightly swollen, with edges slightly everted. The pulp was grayish-red in color and a moderate amount of it could be scraped away. Neither the lymph follicles nor the trabeculae were visible, the surface being homogeneous in appearance. Microscopic examination of the sections revealed

large numbers of phagocytic cells scattered everywhere which contained many Leishman-Donovan bodies (Fig. 7). In the pulp there were also large numbers of small and medium-sized plasma cells, numerous small lymphoid cells and a few large lymphoblasts. The follicles contained fewer of the parasitized cells. Occasional follicles showed areas of scar tissue.

The bone marrow of the ribs and vertebræ was dark red. The entire cavities of the femur and fibula on one side were filled with fairly solid, red marrow. Microscopically the marrow was very cellular. It showed large numbers of macrophages, containing many Leishman-Donovan bodies (Fig. 8). There was also some phagocytosis of red blood corpuscles by the macrophages. There were fair numbers of medium-sized cells having rounded nuclei and weakly acidophilic cytoplasm, among which a few mitotic figures were present. Very few late myelocytes and mature leukocytes could be found. Few eosinophilic leukocytes were present. The marrow was indeed poor in granulocytes. Plasma cells and small lymphoid cells were quite numerous. Megakaryocytes were present. Nucleated red cells were not conspicuous, although all stages in development could be seen.

There was moderate to slight general lymph node enlargement and many of the nodes were dark red in color. This redness was due to congestion in the blood capillaries and hemorrhage into the lymph sinuses. There was moderate hyperplasia of the reticuloendothelial cells and of the young lymphoid elements. Numerous plasma cells were present. No Leishman-Donovan bodies could be found either in the lymph nodes or the tonsils. This was surprising in view of the heavy infection in the spleen and bone marrow.

Summary. An advanced case of kala-azar in a boy of 9. There were extreme leukopenia and total absence of granulocytes in the peripheral blood. Period of observation was short. The post-mortem findings showed tremendous proliferation of macrophages which had ingested the Leishman-Donovan bodies. The bone marrow was poor in granulocytes.

Comment on Case 4. From clinical, laboratory and necropsy findings it is certain that this is a case of kala-azar. The extreme leukopenia and total absence of the granulocytes are remarkable. Strong¹ mentioned the fact that the reduction of neutrophils in kala-azar in children is more marked than in adults, for these cells may be decreased to 5% of the total white blood cells. It is interesting to note that the smears obtained from antemortem puncture of the spleen and the sections of the spleen and bone marrow were packed full of big, phagocytic cells which contained the causative agent of kala-azar. Hu and Cash² suggested that the anemia in kala-azar is myelophthisic in the sense that there is a crowding out of the blood-forming tissue by the tremendous increase of macrophages. We may speculate here that the extreme leukopenia and the total absence of the granulocytes from the peripheral blood may be, at least in part, the result of this process.

Treatment of Acute Agranulocytosis. The treatment of acute agranulocytosis occurring as a complication of kala-azar or of pyogenic infection, or as a part of the disease agranulocytic angina, is

unsatisfactory. The mechanism of the development of agranulocytosis is not known and there is no specific therapy. It is always a problem whether or not to give transfusions of blood. It is not generally accepted that in agranulocytic angina they decrease the mortality significantly. In untreated cases of agranulocytic angina the mortality is about 75%, whereas 64% of patients treated by means of transfusions of blood die.³ It is conceivable that transfusions of large amounts of blood may act to depress the development of granulocytes in the bone marrow and, therefore, may be contraindicated.

Exposures to small doses of Roentgen rays have been used in the treatment of agranulocytic angina by several investigators, notably by Friedemann and Elkeles.⁴ The collected series of cases by Taussig and Schnoebelen³ reveal a mortality of 53% when this treatment was used. The administration of diphtheria antitoxin, antistreptococcus serum, injections of foreign proteins, of neoarsphenamin, of liver extract and the use of various other remedies have their adherents, but the cases treated have been so few and so inadequately controlled that one cannot properly evaluate the advantages or disadvantages of such procedures.

It has been known for many years that the administration of nucleic acid and some of its derivatives to animals will bring about an increase of neutrophils in the blood. Reznikoff⁵ has recently reported that certain derivatives of nucleic acid, the purine bases, adenin and guanin, when given intravenously to patients suffering from agranulocytosis, have the power of raising the peripheral neutrophil count. With such treatment, fully described by the author, a mortality of only 27% is reported in a series of 35 cases.

Jackson, Parker, and Taylor⁶ have utilized another derivative of nucleic acid designated Pentnucleotide. In a series of 54 patients they experienced a mortality of 30%.

We have treated 2 of our cases of acute agranulocytosis complicating kala-azar by intramuscular injections of Pentnucleotide, with satisfactory results in 1 (Case 1) and no apparent effect in the other (Case 3).

It would appear from the above data that the administration of pentose nucleotide or of purine bases derived from nucleic acid offers by far the most satisfactory treatment not only for agranulocytic angina, but also for conditions of agranulocytosis the result of pyogenic infection or of chronic benzene poisoning. For details concerning the administration of these drugs the papers referred to should be consulted.

There are certain other points in the general and local treatment of patients suffering from agranulocytosis which have been found of value and are tabulated below:

1. Strict respiratory isolation from the onset. All attendants or visitors having recent respiratory infections should be excluded.



FIG. 7.—Case 4. Photograph of section of spleen showing large number of Leishman-Donovan bodies within macrophages. ($\times 1290$.)

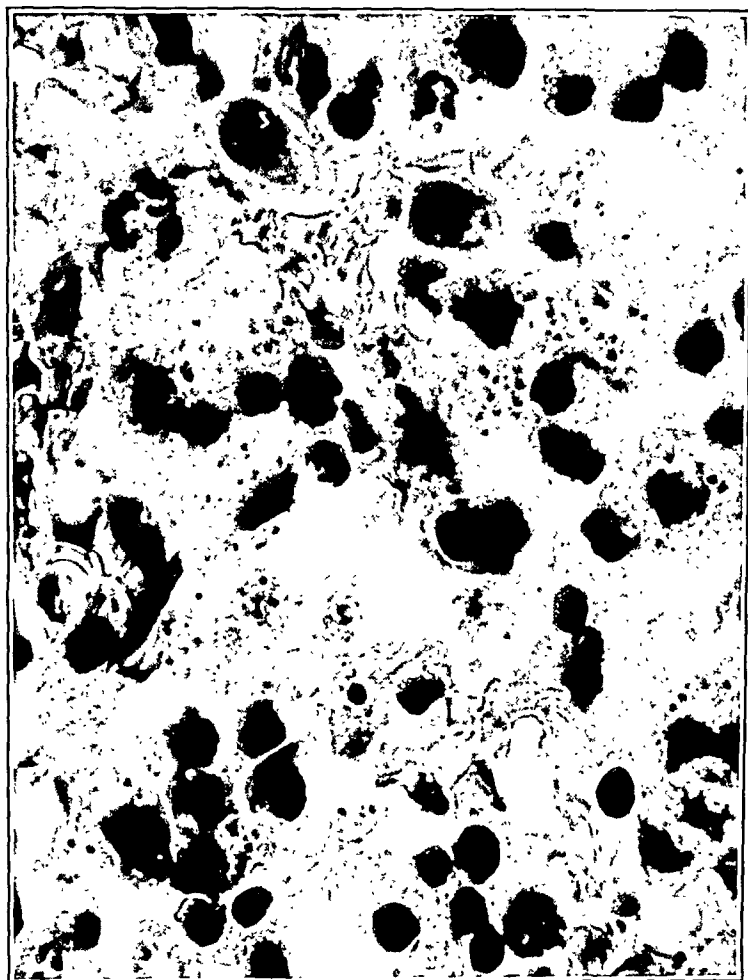


FIG. 8.—Case 4. Photograph of section of the bone marrow of the rib showing many Leishman-Donovan bodies within macrophages. ($\times 1290$.)

2. If the attack is associated with treatment by means of drugs (antimony, arsphenamins), such medication should be withheld.

3. Liquid or very soft solid diet containing generous amounts of cod-liver oil, orange juice and other essential food factors should be the diet of choice.

4. Fluids should be taken in liberal amounts.

5. Mild cleansing mouth washes at frequent intervals. The alternate use of hydrogen peroxid (1.5% to 3%) and of saturated solution of sodium perborate is recommended.

6. Frequent painting of lesions of the mucous membranes with aqueous solution of gentian violet (1%) seems to be of value.

Although little is known concerning the etiology or the specific treatment of agranulocytic angina or of acute agranulocytosis of other origin, it appears that appropriate therapy with derivatives of nucleic acid may be a life-saving procedure.

Discussion. The condition of acute agranulocytosis as observed in the above cases is not merely an exaggeration of the usual state of leukopenia in kala-azar. It occurs as an unexplained phenomenon characterized by an abrupt and transient disappearance or marked decrease of the polymorphonuclear cells from the blood. This complication apparently bears no relation to the existing state of anemia or leukopenia. Neither does the relative number of neutrophils existing in the blood prior to or after the subsidence of an attack of acute agranulocytosis have any apparent relation to the episode.

Attention is called to a case reported by Tso⁷ which differed from 3 of the cases studied by us in that the latter exhibited acute agranulocytosis, whereas Tso's case represented a more chronic and usually less severe granulocytopenia which, as Strong¹ pointed out, occasionally occurs in children afflicted with kala-azar. The period of observation in our fourth case was too short to ascertain whether there existed acute or chronic agranulocytosis. It would appear from our studies that acute agranulocytosis in kala-azar is much more common than is ordinarily supposed. This may have some bearing on another complication of kala-azar, namely, noma or cancrum oris, which not uncommonly occurs in patients suffering from this disease. It is conceivable that during the phase of acute agranulocytosis, which is unrecognized and untreated, the resistance of the patient is so lowered that the appearance of noma as in our Case 4 with its rapid and extensive ulceration of the tissues is rendered possible.

Agranulocytosis, in our experience, has been observed only in a few diseases. It is rare in aplastic anemia and in leukemia and is uncommonly encountered in the course of pyogenic infections, but occurs as the chief characteristic of the disease agranulocytic angina (Fig. 9). The agranulocytosis occasionally found associated with aplastic anemia and with leukemia usually is gradual in onset

ness. These symptoms become more intense as the degree of agranulocytosis increases and as its duration is prolonged.

The occurrence of acute agranulocytosis in patients under observation suffering from kala-azar has rendered possible further observations on these early symptoms and signs associated with the disappearance of granulocytes from the blood. Such observations have led us to the concept that there is a characteristic syndrome which may be associated with acute agranulocytosis (Fig. 10). This

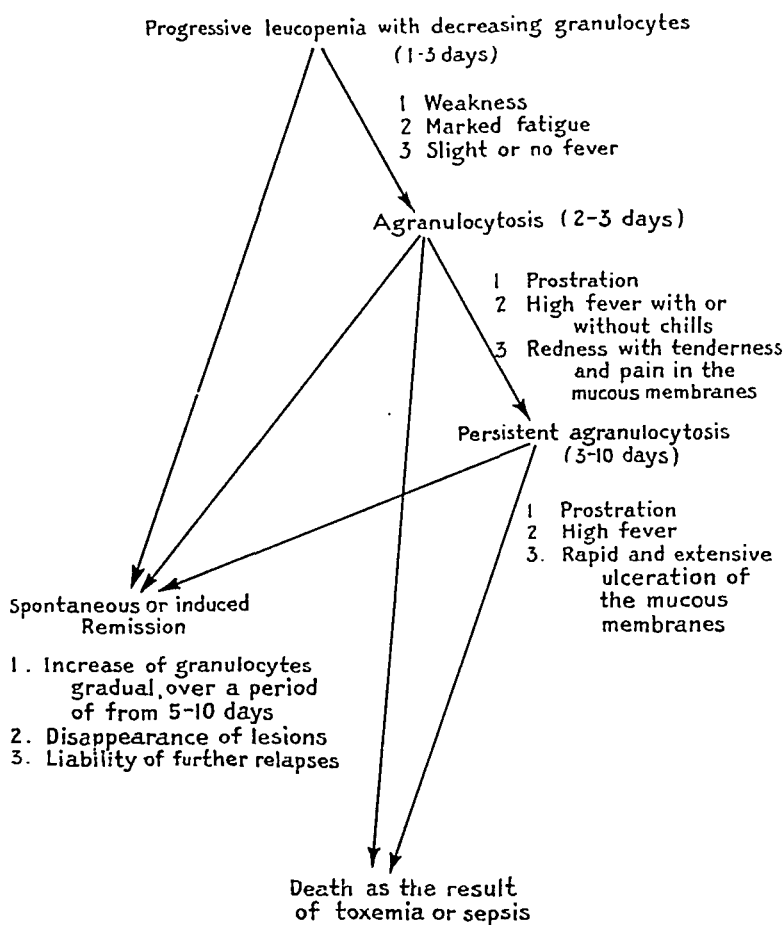


FIG. 10.—Syndrome of acute agranulocytosis as it occurs in agranulocytic angina, kala-azar and pyogenic infections.

syndrome is less conspicuous when it occurs as a complication of kala-azar than when it is associated with agranulocytic angina owing to the fact that attacks of the latter disease come on abruptly during a period of good health whereas the agranulocytosis of kala-azar occurs in patients who are already quite ill.

The first clinical manifestations of this syndrome are weakness and a feeling of exhaustion coming on rather rapidly over a period of from 12 to 72 hours. White blood cell counts at this period show

an increasing leukopenia with a decrease in number of granulocytes. The symptoms become more intense and the leukocytes frequently decrease to from 500 to 2000 cells per c.mm. with a total absence of, or the presence of very few neutrophils. After from 24 to 96 hours more alarming symptoms appear, consisting of high fever, redness and tenderness of the mucous membranes, soon followed by rapidly extending ulceration accompanied by localized pain and marked general discomfort. Unless there occurs, either spontaneously or as the result of treatment, an increase in the number of neutrophils, the symptoms and signs progress and the patient succumbs often as the result of infection. On the other hand, if the leukopenia subsides and the granulocytes progressively increase before severe secondary infection has occurred, a remission takes place in which there is rapid recovery.

The fact that in 2 of our cases acute agranulocytosis occurred during the course of treatment with Neostibosan and after the administration of a considerable amount of the drug suggests that the medication might have played some part in the precipitation of the attack. Recently 2 additional cases of acute agranulocytosis of kala-azar not reported in this communication, but which were comparable to Cases 1 and 2, have occurred.* The agranulocytosis in 4 of the 6 cases came on acutely near the end of the proposed course of treatment with Neostibosan. Because of this theoretic implication we have studied in animals the effects on the blood and blood-forming organs of large and repeated doses of Neostibosan and urea stibamin.† The report of this work will be published elsewhere, but it may be stated here that no significant changes could be demonstrated in the blood of these animals. Further studies of additional cases may give some clue as to the etiology of the agranulocytosis, but at present no satisfactory explanation is available.

Summary. Agranulocytosis occurred in 4 of 26 consecutive patients suffering from kala-azar. In 3 of these the agranulocytosis was acute, in 1 of which it was recurrent. The period of observation of the fourth case was too short to determine whether the attack was acute or chronic. Two additional cases were observed, but not reported in detail.

Acute agranulocytosis is a common and previously unrecognized complication of kala-azar. It is only as the result of frequent and careful studies of the blood that this complication may be detected and appropriate treatment given.

The treatment of acute agranulocytosis is discussed.

* Since the preparation of this manuscript 2 additional patients have been observed in whom acute agranulocytosis has occurred as a complication of kala-azar. One of these 2 patients died during the attack on the 4th day of the agranulocytosis and in spite of vigorous treatment with Pentnucleotide.

† Urea stibamin—carbamid salt of p-amino-phenyl stibimic acid containing antimony in the pentavalent form.

A syndrome of acute agranulocytosis as it occurs in kala-azar, pyogenic infections and agranulocytic angina is described.

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HEART DISEASE IN THE MIDDLE WEST.***(INCIDENCE AND ETIOLOGY OF 1646 CASES AT THE COOK
[COUNTY HOSPITAL.]**

BY NATHAN FLAXMAN, M.D.,

CLINICAL ASSISTANT IN MEDICINE, LOYOLA UNIVERSITY SCHOOL OF MEDICINE
AND MT. SINAI HOSPITAL, CHICAGO, ILL.

SURVEYS of the incidence and etiology of the various forms of heart disease have been reported from a number of centers, but no detailed study has been made in the Middle West. Carr,⁴ in a brief summary of the files of the Cook County Hospital, reported that, in 1923, there were 1236 cases of cardiac disease with 325 deaths. Gethner,⁸ without submitting statistics, said that in Chicago, where everyone is under unusual strain, the increase in mortality from cardiovascular disease is $1\frac{1}{2}$ times greater than that of the whole United States. In 1932, the death rate was 1090 per 100,000 population for the United States registration area.¹¹ Heart disease led all causes and accounted for 19.2% of the deaths. Riesman,¹¹ in summing up the heart situation recently, stated that whether or not there is an alarming increase in deaths from organic heart disease, the fact that heart disease stands at the head of the list makes it a definite problem in health conservation in the sense that efforts should be made to postpone as late as possible death from this cause.

This study covers a period of 18 months, from January 1, 1932, to June 30, 1933. The list of patients entering the Cook County Hospital under the diagnoses of organic heart disease, decompensated heart, auricular fibrillation, coronary sclerosis, mitral stenosis, endocarditis and similar cardiac diagnoses was obtained each day from the cards in the Admitting Room. Each patient was

* Work done while an intern at the Cook County Hospital, Chicago, Ill.

followed up as soon as possible to ascertain whether the diagnosis was correct. Practically all were submitted to individual study during the stay in the hospital. These figures represent only the incidence and etiology of heart disease in patients admitted to the Cook County Hospital. During this period, 235,193 patients applied for admission to the hospital and 95,629 (40%) were admitted. In this group of admissions, 4600 (4.8%) entered with a cardiac diagnosis. A follow-up of these 4600 cases in the hospital, along with the locating of cardiacs in the wards with a non-cardiac admitting room diagnosis, revealed that only 1646 (1.7%) patients had definite organic heart disease. It is well to emphasize that these 1646 patients were admitted 2800 times to the hospital during the 18-month period. The criteria followed for the classification and diagnosis of heart disease were those approved by the American Heart Association.¹⁸ Most of the criteria are definite except in cases which have a hypertensive or arteriosclerotic etiology. In this study all cases that presented clinically gross arteriosclerosis without hypertension were included in the arteriosclerotic group. Cases which presented evidences of myocardial insufficiency with hypertension and no clinical evidence of arteriosclerosis were included in the hypertensive group. All cases that presented both gross arteriosclerosis and hypertension were included in the group termed arteriosclerosis with hypertension. In this group it is very likely that the hypertension has no relation to the arteriosclerosis. These patients probably have outlived the hypertension and reach the stage where they develop arteriosclerosis. The term senescent or degenerative heart disease does not and should not include the hypertensive etiology. Hypertension appears to be a separate and distinct entity unrelated not only to arteriosclerosis but also to syphilis, rheumatic heart disease and to thyrotoxicosis.

TABLE 1.

General survey.	No. of patients and per cent.
Applied for admission	235,193
Hospital admissions	95,629 (40%)
Deaths, entire hospital	9,276 (9.7% of admissions)
Medical admissions	22,942 (24% of admissions)
Medical deaths	4,303 (19% of medical admissions)
Total hospital autopsies	1,898 (20% of all deaths)
Organic heart disease	1,646 (1.7% of all hospital admissions) (7.2% of medical cases)
Improved	971
Unimproved	53
Deaths	622 (6.7% of all deaths) (14.4% of medical deaths)
Autopsies	304 (16% of all autopsies)

Incidence of Heart Disease. The 1646 cases of organic heart disease were 1.7% of the total hospital admissions and only 7.2% of the medical cases, a low figure and certainly no cause for great alarm (Table 1). On discharge, 971 were improved, 53 unimproved

and 622 (38%) died in the hospital. This constituted 6.7% of all the hospital deaths from all causes and 14.4% of all the medical deaths. The basic cause for the high mortality was the economic situation of the patient. Many of these patients were discharged from the hospital well compensated and in good condition only to return within a month or 6 weeks in a terminal condition because they had to return to work to live or because they had no work and had great difficulty just living.

Age Incidence. Of the white patients, 52.1% were between 40 and 60 years of age. The common decades were the 6th for the white male and the 5th for the white female. Of the colored patients, 56.8% were in the 40-to-60-year group, but the 5th decade was the most common period for heart disease to occur in this group. Of the 1646 patients, 54% were in the 40-to-60-year group.

TABLE 2.—PERCENTAGE OF THE AGE GROUPS.

Ages.	White.				Colored.				Both.	
	M	F	T	%	M	F	T	%	Totals.	%
14-20 . .	19	15	34	2.9	5	3	8	1.7	42	2.6
21-30 . .	30	22	52	4.4	24	16	40	8.9	92	5.6
31-40 . .	87	48	135	11.1	54	30	84	18.3	219	13.1
41-50 . .	190	74	264	22.1	117	43	160	34.5	424	26.0
51-60 . .	305	49	354	31.0	82	21	103	22.3	451	28.0
61-70 . .	203	46	249	21.2	43	9	52	11.3	301	18.0
71-80 . .	72	13	85	7.2	12	0	12	2.6	97	5.8
81-90 . .	10	2	12	0.1	1	1	2	0.4	14	0.9
Totals . .	916	269	1185	100.0	338	123	461	100.0	1646	100.0

Etiologic Factors. The most common cause was hypertension, alone or in combination with another factor. Table 3 indicates that it was present in 57% of the cases; in 53.6% of the white patients and 60.4% of the colored patients. The 4 main groups, hypertensive, arteriosclerotic, rheumatic and syphilitic involvement, accounted for 90% of the cases; 88.4% of the white and 94.5% of the colored patients.

Arteriosclerosis. All of the 128 (7.2%) patients were 61 years and over, except 13 white males, 12 of whom were in the 51-to-60-year group and 1, the youngest, was 43 years of age. On discharge, 75 were improved, 4 unimproved and 49 died in the hospital. Twenty-four autopsies were performed. In spite of the advanced age of most of these patients the hospital mortality was only 39%.

Arteriosclerosis With Hypertension. Gross arteriosclerosis with blood pressure readings above 150/100 was found in 163 (9.9%). All of these patients, except 12, were above 61 years of age. Probably these patients have outlived the damaging effects of the hyper-

tensive state and reached the age where the arteriosclerotic changes began to manifest symptoms clinically. On discharge, 99 were improved, 7 unimproved and 56 died (34%).

Subacute Bacterial Endocarditis. There were 42 patients (2.7%) with this affection, although 2 patients had the endocardial infection other than of the valve. One had involvement of the left side of the interventricular septum with perforation into the right ventricle, and the other had a verrucous aortitis superimposed upon a syphilitic aortitis. The ages varied from 14 to 70 years. Four patients were discharged from the hospital, all after long periods of time. Thirty-eight patients died in the hospital (90%), with autopsies on 35.

TABLE 3.—PERCENTAGE OF ETIOLOGIC FACTORS IN THIS STUDY.

Probable etiology.	White.				Colored.				Both.	
	M	F	T	%	M	F	T	%	T	%
Arteriosclerosis	101	18	119	10.0	7	2	9	1.9	128	7.2
Arteriosclerosis with hypertension	118	15	133	11.1	27	3	30	6.6	163	9.9
Bacterial	22	10	32	2.9	3	7	10	2.1	42	2.7
Pulmonary emphysema	23	2	25	2.1	1	0	1	0.2	26	1.6
Hypertension	376	105	481	40.5	163	60	223	48.5	704	43.0
Rheumatism	134	81	215	18.3	20	23	43	9.4	258	15.8
Rheumatic with hypertension	6	3	9	0.7	3	2	5	1.0	14	0.9
Syphilis	75	2	77	6.5	92	12	104	22.8	181	10.9
Syphilis with hypertension	12	3	15	1.3	13	7	20	4.3	35	2.2
Thyrototoxic	18	18	36	3.0	2	6	8	1.6	44	2.6
Unknown	26	2	28	2.3	3	0	3	0.6	31	1.9
Miscellaneous	5	10	15	1.3	4	1	5	1.0	20	1.3
Totals	916	269	1185	100.0	338	123	461	100.0	1646	100.0

Pulmonary Emphysema. The etiologic factor appeared to be confined to the white patients as a cause of myocardial insufficiency. Of 26 patients (1.6%), only 1 was colored. In practically all of these patients the emphysema was the result of a dusty occupation over a period of many years. The hospital mortality was 50%, and autopsies were performed in 8 of the 13 cases.

Hypertension (Without Gross Arteriosclerosis). This factor accounted for 43% of the cases alone and was present in 57% of all the cases. On discharge, 448 patients were improved and 18 unimproved. There were 238 deaths (32%). Only 88 autopsies were performed which, if considered alone, would not give a true picture of the part hypertension takes in the etiology of heart disease.

Rheumatic Heart Disease. The largest number of these 258 patients (15.8%) were in the 4th decade. There were 76 deaths (30%) and autopsies were performed in 32 cases.

Rheumatic Heart Disease With Hypertension. This group of 14 patients were not unlike the above group except that the blood pressure readings were above 150/100. There were 6 deaths (43%), and autopsies confirmed the diagnoses.

Syphilitic Heart Disease. This appeared a decade earlier in the 104 colored patients than in the 77 white patients. On discharge, 78 patients were improved, 1 unimproved and there were 102 deaths (56%).

Syphilitic Heart Disease With Hypertension. This combined etiology, present in 35 cases (2.2%), had a mortality slightly lower than the previous group. There were 18 deaths (51%), and autopsies were performed in 15 cases.

Thyrotoxic. Forty-four patients (2.6%) presented cardiac symptoms and findings on a thyrotoxic basis; 13 patients died in the hospital (30%).

TABLE 4.—PERCENTAGE OF HEART DISEASE PREVIOUSLY REPORTED.

Hospital or city and year.	Hospital admissions.	Medical admissions.	Autopsy records.	%
Galveston, Texas, ¹³ 1920-1926 . . .	25,816	3.5
Massachusetts General, ¹⁵ 1926 . . .	8,226	6.0
		2,766	...	18.0
Cincinnati, ¹ 1926	9,570	7.2
Pacific Northwest, ⁵ 1928	28,661	12.0
		13,258	...	26.0
Salt Lake City, ¹⁴ 1927-1930 . . .	16,519	2.9
Galveston, Texas, ¹² 1927-1930	3.3
				16.3
Vanderbilt Univ. Hospital, ¹⁰ 1931	4.1
Cincinnati, ⁹ 1927-1931	2344	17.0
Detroit, ² 1932-1933	1535	20.0

Thyrotoxic With Hypertension. Seven patients had hypertension in addition to the thyrotoxic heart disease. Neither factor seemed to have any relation to the other. Three patients were discharged as improved, 3 as unimproved and 1 male died in the hospital.

Unknown. In a group of 31 cases (1.9%) no known etiologic factor or factors were evident to account for the myocardial insufficiency. Five autopsies were performed of 8 deaths, and the etiology in these cases remained undisclosed. In all studied statistics of this type a small group of patients presented myocardial insufficiency to which no known etiologic factor could be attributed.

Miscellaneous. This included 4 cases of myocardial insufficiency attributable to anemia, 3 cases of congenital heart disease, 1 each of diphtheria, scarlet fever and toxic myocarditis, the 3 female patients with myxedema and the 7 patients previously mentioned

who had thyrotoxic myocarditis with hypertension. Only 1% of the cases of organic heart disease fall into this group.

Comment. For large general hospital admissions the incidence of organic heart disease varies from 1.7% for the Cook County Hospital to 12% for the Pacific Northwest. The latter figure is high, as Coffen⁵ indicated, because hospital records are only satisfactory as to the incidence of cardiovascular disease as compared with the total medical admissions. The incidence was, of course, greater where only the medical admissions were considered, the lowest, 7.2%, at the Cook County Hospital and the highest was 26% from the Pacific Northwest.⁵

TABLE 5.—COMPARATIVE REPORTED PERCENTAGE OF ETIOLOGIC FACTORS.

Locality.	Arterio-sclerosis	Bac-terial	Hyper-tension.	Rheu-matic.	Syph-ilis.	Thyro-toxic.	Total cases.
Boston ³	15.5	0	19.5*	46.4	10.6	0.1	600
New England ¹⁷	23.1	0	0.1	44.5	9.0	0.0	1001
Virginia and Boston ¹⁶	7.3	0	46.0	22.0	21.4	0.0	623
Galveston, Texas ¹³	13.7	1.5	47.7	7.3	19.3	1.3	915
New England ¹⁵	35.7	1.9	29.2	39.5	3.9	2.9	2421
Pacific Northwest ⁶	56.0	1.0	...	6.1	3488
Salt Lake City ¹⁴	21.1	0.2	14.9	44.0	1.1	9.3	867
Cincinnati ⁹	41.0	9.0	...	3.0	14.0	...	398
Galveston ¹²	20.2	...	57.2	...	12.7
Detroit ²	15.0	13.0	40.0	11.0	6.0	...	1535
New York State ⁸	8.8	...	20.1	27.2	4.6	...	1934
Tennessee ¹⁰	68.0†	...	68.0†	10.3	6.0	...	645
Washington, D. C. ⁷	19.0	1.4	55.6	6.0	10.0	2.5	1200
Chicago (this study)	17.1	2.7	43.0	16.7	13.1	2.6	1646

* Classified as nephritic in the original study.

† Arteriosclerotic-hypertensive group combined.

The most common age group was the 40-to-60-year period. The average age was 53 years for the white patients and 44 years for the colored patients. There were a negligible number of patients between the ages of 14 and 20 years, but from this age upward the number of patients with heart disease gradually increased until it reached the peak in the 50-to-60-age group. In this decade, hypertensive and syphilitic heart disease were at their height, rheumatic heart disease took its toll of those that had suffered in the past decade and arteriosclerotic heart disease was beginning to manifest itself.

The outstanding etiologic factor in the causes of heart disease in the adult is hypertension. Comparative study of 14 such surveys from the United States give hypertension as the leading cause in 8 of the 14 reports. Rheumatic heart disease is given as the leading cause in 5 and arteriosclerotic heart disease in the other report. Three reports from the New England States^{3,15,17} give rheumatic

heart disease as the leading cause, as do one each from the Rocky Mountain region¹⁴ and the state of New York exclusive of New York City.⁶ Arteriosclerotic heart disease, as the leading cause, is based on autopsy statistics from the Cincinnati General Hospital.⁹

The next important cause is arteriosclerosis and, with hypertension, is the main cause in most reports. Rheumatic heart disease follows these in frequency, and syphilis is the fourth important cause. Other factors are present in only a small number of cases. It is apparent that statistics on the incidence and etiology of heart disease must be classified on a better basis. The most representative statistics are those based on large general hospital admissions. In spite of the low value generally conceded to vital statistics and the high value placed on autopsy figures, the percentage of recorded heart disease is approximately the same. Vital statistics place the percentage of deaths due to organic heart disease at 20%. Autopsy figures from four large general hospitals give an average of 18%.

Summary. 1. The incidence of organic heart disease at the Cook County Hospital for the 18-month period, from January 1, 1932, to June 30, 1933, was 1.7% of the total hospital admissions and 7.2% of the medical admissions.

2. Of the 1646 patients, 38% died in the hospital during the stated period; this was 6.7% of the hospital deaths and 14.4% of the medical deaths.

3. In this study the common age for heart disease was the 40-to-60-year period; it occurred most frequently in the 6th decade in the white patients and in the 5th decade in the colored patients.

4. Hypertension was the most common cause of organic heart disease regardless of the race or sex.

5. Arteriosclerotic and rheumatic heart disease were more common in the white patients.

6. Syphilitic and hypertensive heart disease were more common in the colored patients.

7. Arteriosclerotic heart disease was 5 times more common in the white patients.

8. Pulmonary emphysema as a cause of myocardial insufficiency was practically confined to white males.

9. Rheumatic heart disease was twice as frequent in the white patients.

10. Syphilitic heart disease was 4 times as frequent in the colored patients.

11. Hypertensive, arteriosclerotic, rheumatic and syphilitic heart disease accounted for 90% of the cases of organic heart disease.

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A STANDARDIZED EXERCISE TOLERANCE TEST FOR PATIENTS WITH ANGINA PECTORIS ON EXERTION.*

BY JOSEPH E. F. RISEMAN,

ASSISTANT IN MEDICINE, HARVARD MEDICAL SCHOOL AND BETH ISRAEL HOSPITAL,

AND

BEATRICE STERN,

RESEARCH ASSISTANT, BETH ISRAEL HOSPITAL; BOSTON, MASS.

(From the Medical Research Laboratories of the Beth Israel Hospital and the Medical Department of the Harvard Medical School.)

ALTHOUGH our knowledge of angina pectoris has increased considerably since its first description by Heberden,¹ the diagnosis still rests entirely upon a careful evaluation of the patient's own description of his subjective sensations. We have at our disposal few or no objective criteria with which to confirm the diagnosis: physical examination and Roentgen ray of the heart may reveal nothing of diagnostic importance; the electrocardiogram may be perfectly normal in some cases, while in other instances trivial variations may be of unrecognized significance.² Although the typical symptom complex is easily recognized, there are variations which are important, taxing the judgment of the most able clinicians. It is not surprising, therefore, that patients with angina pectoris are often incorrectly treated for peptic ulcer, neuritis or other diseases,

* This study was aided by a grant from the William W. Wellington Memorial Research Fund of the Harvard Medical School. It is the thirteenth study of the treatment of patients with congestive heart failure and angina pectoris by total ablation of the thyroid.

or that many patients supposedly suffering from angina pectoris really have no organic heart disease.

In addition to the pitfalls in diagnosis, there are difficulties in estimating accurately the severity of the disease, in evaluating the progress of the condition and the results of therapy. These difficulties arise from the variability of the condition under which attacks are precipitated in daily life, their irregularity in frequency, the effect of suggestion, the subconscious self-imposed limitation in activity and the necessity of relying entirely on the patient's impression. In many individuals temporary improvement occurs during the warm months and may be interpreted erroneously as the result of therapy.

Because observation of the patient during an attack would be helpful in diagnosis, certain methods of precipitating anginal attacks have been proposed during recent years. The subcutaneous injection of epinephrin³ is not without danger⁴ and may produce anginal attacks in patients not afflicted with this condition.⁵ The precipitation of attacks by the production of anoxemia⁶ is undoubtedly of diagnostic value. Neither method produces anginal attacks under conditions which have a close clinical counterpart, nor do they permit accurate evaluation of the severity of the spontaneous attacks or of the ease with which they are precipitated in daily life. Wayne and La Place⁷ have recently reported studies on angina pectoris of effort, thus utilizing a physiological stimulus which normally causes anginal attacks.

Early in 1933, in connection with the treatment of patients with angina pectoris by total ablation of the thyroid gland, we were confronted with the necessity of confirming the diagnosis of angina pectoris, of determining the severity of the symptoms and of evaluating the benefits of this therapeutic measures.⁸ A simple and safe method was sought for the production of anginal attacks under conditions comparable to those producing attacks in daily life. Such a method to be of value in diagnosis should precipitate angina pectoris in the vast majority if not all patients with this condition, but should not cause attacks in patients not suffering from this disease. To be of help in the evaluation of therapy, the method should give objective evidence of the patient's condition and should yield substantially the same results on repetition.

Although attacks of angina pectoris may occur when the patient is at rest or even asleep, the majority of patients develop angina on exertion or emotion. The influence of the mental state of the individual is of undoubted importance, but this factor is difficult to measure or reproduce. The amount of exercise which precipitates an attack in a given individual appears to vary considerably from time to time; but the clinical histories of these patients suggest several possible causes for these variations. These include type and rate of exercise, temperature of the environment, excitement,

food, medication, recent attacks of angina and recent exertion. We have studied the influence of each of these factors, and on the basis of these studies have evolved a method for the production of anginal attacks which seems to fulfill the requirements outlined above. This method has been in use for over a year and has given satisfactory results. Our first experience with the test has been reported.⁸ The purpose of this communication is to describe the method in detail and to report the results of our studies to date.

Factors Which Influence the Patient's Exercise Tolerance. *Type of Exercise.* The type of exercise used in an exercise tolerance test should be one with which the patient is familiar and which requires little or no training. The bicycle ergometer in our hands has given quite variable results presumably because the ordinary hospital patient is not accustomed to this type of exercise and, therefore, requires considerable training and practice before he can perform the work satisfactorily. This is especially true of patients in the age group in which angina pectoris is most frequent.

TABLE 1.—THE AMOUNT OF WORK NECESSARY TO PRODUCE ANGINA PECTORIS ON THE TWO-STEP STAIRCASE COMPARED WITH THE AMOUNT NECESSARY WHEN EXERCISING ON ORDINARY FLIGHTS OF STAIRS.

Case No.	Weight, pounds.	Two-step staircase (each trip 18 inches high).			Ordinary staircase (each flight 20 to 22 steps, each step 7½ inches high).			
		Temp. °F.	Amount of work.		Temp. °F.	Amount of work.		
			Trips.	Foot pounds.		Flights.	Steps.	Foot pounds.
3*	173	53-56	12-13	3,100- 3,400	63-69	2.8	61	6,250
5*	156	52-58	18-24	4,200- 5,600	77	1.8	37	3,400
6*	147	58	18-22	3,950- 4,850	78	1.9	41	3,600
9	110	51-54	22-26	3,650- 4,300	40-60	7.0	152	10,000
23	146	46-51	38	8350	48-64	4.9	103	8,900
26	165	48-58	36-45	8,900-11,200	52-54	5.7	124	12,100
21	169	52-58	34-38	8,650- 9,650	72	9	184†	18,400
29	143	50-56	58-66	12,500-14,200	72	9	184†	15,700

* In these individuals variation in temperature of the environment caused no great difference in the amount of work necessary to produce angina pectoris.

† No attack of angina pectoris was produced.

The ordinary staircase is unsuitable for exercise tolerance tests for several reasons. Exercise on a long staircase may precipitate severe angina when the patient is half way up the flight, and so he may be temporarily unable to go up or down and be forced to rest on the staircase. Variations in the height of the steps, the length of the flights of stairs and the size of the landings prevent comparing the results obtained in different buildings. Furthermore, the number of stairs required (often 4 or more flights, Table 1) is not available in all buildings. Finally, the temperature of a stair-

well is difficult to regulate, especially during the summer months and, as will be shown, the temperature of the environment in which the exercise is performed greatly influences the amount of exercise necessary to product an attack of angina.

In order to overcome these objections we have used a two-step staircase similar to that described by Master and Oppenheimer⁹ (Fig. 1). The exercise of walking up and down steps is familiar to the patient and requires no training. The amount of exercise can be varied readily. When the patient develops an attack of angina, he can rest safely in the very room in which the exercise is performed. Being portable, the staircase can be moved readily to a room with regulated temperature. The number of foot pounds of work performed may be estimated roughly by multiplying the patient's weight by the height of the staircase ($1\frac{1}{2}$ feet) and the number of trips performed. This is inexact, however, for it ignores the work done in descent of the staircase.

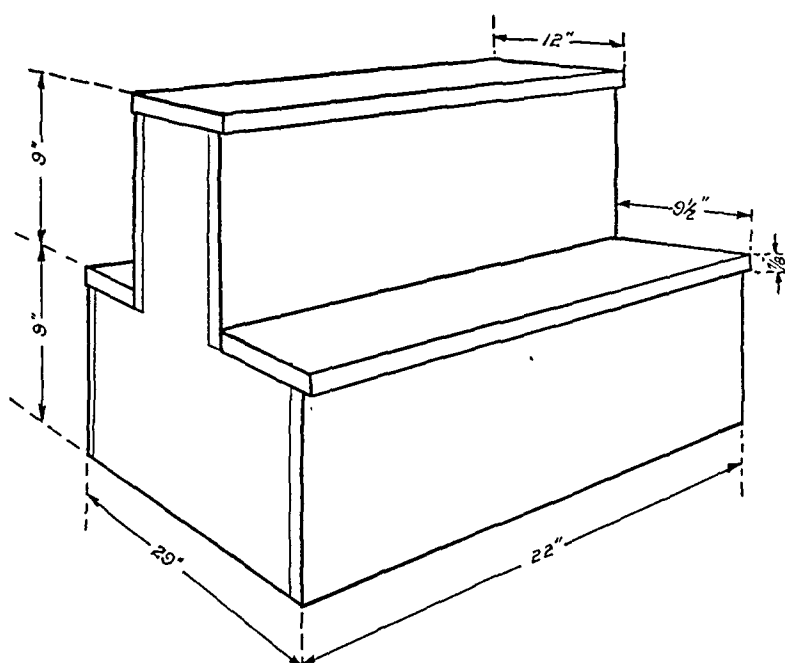


FIG. 1.—Dimensions of the two-step staircase.

We have found that the majority of patients suffering from angina pectoris develop typical attacks when exercising on the two-step staircase under standard conditions. When the test is repeated, the same amount of exercise invariably precipitates an attack in the same individual, providing the standardized conditions are reproduced.

Rate of Exercise. To obviate the necessity for training and to minimize the effect of excitement the patient is allowed to choose

his own rate. The average speed of exercise for all patients was 13 trips per minute.* Only an occasional patient exercised at a rate substantially different. The rate for each individual was reasonably constant even when the test was performed at widely separated intervals of time (Table 2). Doubtless, exercise at much slower or faster rates would give different results.

TABLE 2.—COMPARISON OF THE RESULTS OF THE STANDARDIZED EXERCISE TOLERANCE TEST WHEN REPEATED AFTER AN INTERVAL OF 2 OR MORE MONTHS.

Case. No.	Date.	Temp. of room, °F.	Duration of exercise, min.	Amount of exercise, trips.	Rate of exercise, trips per min.
13	4/ 3/33	56	1.5	22	14½
	6/ 2/33	51	1.5	22	14½
4	5/ 5/33	48	1.3	15	12
	7/ 5/33	56	1.2	13	11
30	10/27/33	53	4.9	63	13
	12/22/33	53	5.3	70	13
10	10/27/33	53	2.0	20	10
	1/ 2/34	50	1.9	19	10
11	10/25/33	50	1.8	20	11
	1/11/34	54	2.0	19	9½
2	5/15/33	54	1.3	12	9½
	9/18/33	56	0.5	6	12
21	4/17/33	58	3.0	38	12½
	11/25/33	52	2.8	36	13
24	4/17/33	58	2.7	40	15
	12/22/33	50	3.7	59	16

Excitement. Exercise on the two-step staircase is so similar to acts performed in daily life that the emotional factor is minimized. In 7 out of 30 individuals, however, we found that at the time of the first test angina was developed after considerably less exertion than at subsequent tests (Table 6). This discrepancy was due presumably to excitement and existed only at the time of the first test.

Temperature. The increased frequency of anginal attacks during the cold winter months is well recognized. Measurement of the amount of work that an individual can perform in warm and cold atmospheres is presented in Table 3. Because of convenience, a Barach oxygen chamber was used in most experiments. The chamber was filled with ordinary air and the temperature was maintained roughly between 45° and 55° F. A large refrigerator, of the type available in most hospitals and markets, was used in several tests. The results obtained in the oxygen room and in the refrigerator were identical.

The temperature used did not cause shivering and was not uncomfortable for the patients even when dressed in thin hospital attire. Our patients usually began to exercise within 5 minutes after entering the cold room. More prolonged exposure did not affect the results. None developed angina at rest in the cold room.

* The term "trip," as used here signifies one ascent and one descent of the staircase.

Five of 15 patients showed striking differences in the amount of exercise necessary to precipitate angina at different temperatures (Table 3). Two (Cases 26 and 29) did not develop attacks at room temperatures even though they exercised to the point of exhaustion. Two others (Cases 21 and 27) showed extremely variable results when exercising at room temperatures. Two of these 4 patients (Cases 21 and 29) climbed 9 flights of stairs (average temperature, 72° F.) without angina. The fifth individual (Case 17) developed marked palpitation at room temperature, which prevented continuing the exercise to the point of angina. Each of these 5 patients invariably developed typical attacks of angina pectoris after relatively small amounts of exercise in the cold room.

TABLE 3.—THE EFFECT OF TEMPERATURE ON THE AMOUNT OF EXERCISE NECESSARY TO PRODUCE ANGINA PECTORIS.

Case No.	Temp. of room, °F.	Amount of exercise, trips.	Anginal attacks.
1	49-51	9-11	Present.
	62-64	9-11	Present.
3	53-56	12-13	Present.
	77-83	15-17	Present.
4	48-57	13-15	Present.
	79	18	Present.
5	52-58	15-24	Present.
	73-77	20-24	Present.
6	58	18-22	Present.
	74-76	16-19	Present.
8	48-56	13-21	Present.
	75-76	13-21	Present.
13	50-56	22-26	Present.
	77	24	Present.
14	46-48	26-29	Present.
	82	37	Present.
16	48-56	24-37	Present.
	79-81	30-32	Present.
27	43-48	53-57	Present.
	76-78	44-78	Present.
28	48-56	58-66	Present.
	79	65	Present.
21*	52-58	34-38	Present.
	75	39	Present.
	80	76	Questionable.
	76	100	No attack.
26	48-58	36-45	Present.
	81	40	No attack.
	76	56	No attack.
29*	50-56	58-66	Present.
	78	100	No attack.
	78	229	No attack.
17	46-50	29-30	Present.
	75-76	13-21	Severe palpitation preventing fur- ther exercise; no attack.

* These patients were able to climb 9 flights of stairs (184 steps, each 7½ inches high) at 72° F. without developing angina pectoris.

Effect of Meals. Patients frequently develop angina more readily after a heavy meal. Our standard tests have been performed either in the fasting state or at least 1 hour after a light meal. Under such conditions no important variations in the amount of exercise required to produce attacks were evident. Three patients were tested 20 minutes after a heavy meal. In 2 of these individuals the meal did not influence the amount of work necessary to precipitate an attack, whereas the third patient developed an attack after performing only about two-thirds of his usual amount of work (Table 4).

TABLE 4.—THE EFFECT OF FOOD ON THE NUMBER OF TRIPS NECESSARY TO PRODUCE ANGINA PECTORIS.

Case No.	Fasting, trips.	1 hr. or more after light meal, trips.	20 min. after heavy meal, trips.
8	15	17-21	13
16	27	24-37	25
28	66	58-64	42

TABLE 5.—COMPARISON OF THE AMOUNT OF WORK REQUIRED TO PRODUCE ANGINA PECTORIS UNDER STANDARDIZED CONDITIONS AND WHEN THE TEST WAS AGAIN PERFORMED AFTER 5 TO 10 MINUTES' REST.

Case No	Standardized test, trips.		
	1st test.	2d test.	3d test.
2	12	8	
4	13	20	
13	25	40	
19	35	46	
29	65	147	
	66	154	98*
	58	150	85†
28	64	8	

* On hour after the preceding anginal attack.

† Four hours after the preceding anginal attack.

Effect of Medication. After taking nitroglycerin patients were often able to perform more exercise before developing an attack. For example, one of our patients (Case 30) who regularly developed angina after 63 to 70 trips was able to perform 100 trips 1 hour after taking a $\frac{1}{100}$ -grain nitroglycerin pill.

Effect of Recent Attacks of Angina Pectoris. Many patients develop an attack shortly after going out into the cold, but thereafter may be able to exercise outdoors for hours without experiencing pain. Others find that the first attack predisposes them to subsequent attacks, while still others find that their tolerance for exercise is approximately the same at all times. Similarly, previous exercise or preceding attacks of angina pectoris affected the results of our tests. In 6 patients an attack of angina was precipitated, and after 5 to 10 minutes' rest the test was repeated (Table 5). In 2 of these (Cases 2 and 4) the results of the second test were not significantly different from the first. Three others (Cases 13, 19, 29) were able to do more work than was possible at any

other time. This was especially striking in one patient (Case 29) who was able to do between 2 and 3 times as much work as usual after he had experienced the first attack. This protective effect

TABLE 6.—THE AMOUNT OF EXERCISE REQUIRED TO PRECIPITATE ANGINA PECTORIS IN 34 PATIENTS.*

Case No.	Date of test, 1933 and 1934.	Temperature of room, °F.	Duration of exercise, min.	Amount of exercise, trips.	Case No.	Date of test, 1933 and 1934.	Temperature of room, °F.	Duration of exercise, min.	Amount of exercise, trips.
1 ..	6/20	51	1.2	9	17 ..	9/26	47	2.6	30
	6/21	49	0.8	11		9/27	46	2.3	29
2 ..	5/15	54	1.3	12		9/28	50	2.4	29
	5/18	46	0.5	6	18 ..	7/14	55	1.9	28
3 ..	10/27	53	1.0	12		7/17	58	1.5	24
	11/10	56	1.0	13		7/18	58	1.8	32
4 ..	5/ 1	54	...	6		7/19	60	1.8	32
	5/ 5	48	1.3	15	19 ..	11/ 6	44	1.5	19
	7/ 3	57	1.2	13		11/ 8	49	2.3	35
	7/ 5	56	1.2	13		11/20	56	3.5	31
5 ..	11/10	58	1.2	15	20 ..	12/28	53	1.9	36
	11/20	58	2.2	24		1/ 2	48	2.4	32
	11/27	52	1.4	18		1/ 4	48	2.5	36
6 ..	11/10	58	1.8	22	21 ..	4/17	58	3.0	38
	11/20	58	1.5	18		11/ 4	52	2.0	34
7 ..	11/27	52	1.2	16		11/25	52	2.8	36
	11/28	56	1.6	21	22 ..	10/23	50	2.6	37
	11/29	55	1.8	23		10/28	55	4.0	47
8 ..	11/15	55	2.2	18	23 ..	12/11	46	3.4	38
	11/16	50	2.1	21		12/26	51	3.1	38
	11/17	48	1.5	17	24 ..	4/17	58	2.7	40
	11/20	56	1.2	15		12/22	50	3.5	59
	11/21	55	1.2	13	25 ..	10/27	53	2.7	30
9 ..	12/ 1	51	1.1	22		10/30	47	5.4	44
	12/26	51	1.2	23		12/30	52	5.5	56
	1/11	54	1.0	26		1/13	45	4.0	50
10 ..	10/27	53	2.0	20	26 ..	11/10	58	4.0	40
	12/22	52	1.7	17		11/24	52	3.7	36
	1/ 2	50	1.8	19		1/ 2	48	3.9	45
11 ..	10/23	50	2.4	25	27 ..	10/ 4	46	2.8	39
	10/25	46	1.8	20		10/ 5	43	4.2	57
	1/11	54	2.0	19		10/ 7	48	3.8	53
12 ..	7/17	55	2.0	21		10/ 9	45	3.9	56
	7/18	58	2.3	21	28 ..	11/16	50	2.9	58
13 ..	4/ 3	56	1.3	22		11/17	48	2.9	64
	4/29	53	1.7	22		11/20	56	3.3	66
	4/30	53	2.2	25	29 ..	3/ 2	56	4.4	65
	5/ 1	51	1.8	26		3/12	50	4.3	66
	6/19	50	1.5	22		3/13	50	3.8	58
14 ..	10/23	50	0.8	8	30 ..	10/27	53	4.9	63
	10/28	46	2.1	26		12/22	53	5.3	70
	11/ 2	48	2.1	29	31 ..	10/23	50	0.5	1
	11/ 3	48	2.1	26	32 ..	11/10	48	3.8	33
15 ..	10/27	53	1.3	22	33 ..	11/10	58	3.8	33
	11/20	58	2.3	34	34 ..	10/26	49	2.6	34
16 ..	11/15	55	1.9	24					
	11/16	50	2.5	29					
	11/17	51	3.0	37					
	11/18	48	2.3	27					
	11/21	56	1.8	25					

* There were 27 males and 7 females, with ages varying from 41 to 72.

apparently lasted for several hours. In this individual severe exercise even without the development of an attack apparently had some protective effect. The sixth patient (Case 28) found that on repetition of the test he was able to do only about one-eighth as much work as he usually could accomplish.

A Standardized Exercise Tolerance Test. With a knowledge of the physiologic conditions which cause variations in the amount of exercise necessary to produce an attack of angina pectoris, it is possible to standardize these conditions so that the amount of exercise necessary to produce an attack serves as an index of the severity of the patient's illness. Reproduction of these standardized conditions enables one to test the patient under identical conditions regardless of season or climate, and makes it possible to evaluate the results of therapy. This is the basis of the standardized exercise tolerance test used at the Beth Israel Hospital during the past year. These standardized conditions reproduce the environmental situation which gives rise to angina pectoris in daily life and so permit personal observation of the clinical signs and symptoms under controlled conditions.

Method. The test is performed in a room, the temperature of which is adjusted to between 45° and 55° F. The patient is tested at least 1 hour after a light meal or before breakfast on a day during which he has not experienced an anginal attack. The results are compared with single tests on other days. In patients who have several attacks during the day, it may be necessary to perform the test despite recent angina. In such individuals, repetition of the test at several subsequent dates will reveal whether or not constant results can be obtained under such conditions.

The exercise consists in repeatedly walking up and down the two-step staircase described above (Fig. 1), at a rate which is usual or comfortable for the patient. Dizziness is avoided by having the patient turn toward the same wall at the completion of each trip on the staircase.

The patient continues the exercise until he develops an attack of angina pectoris severe enough to cause him to stop. The number of times the patient mounts the staircase, that is to say, the number of trips performed, is recorded with a tally counter. The rate and the duration of the exercise are measured with a stopwatch.

Results. During the past year over 500 attacks have been studied in 57 consecutive patients, diagnosed as suffering from angina pectoris. Each of the individuals had been studied previously either in the Out-Patient Department or on the medical wards of the Beth Israel Hospital. The diagnoses had been made by various members of the hospital staff and had been based entirely on the clinical findings. In 4 of these patients it was impossible to perform the test because of infirmity or lack of coöperation. The remaining 53 individuals were able to exercise without difficulty, even though many had been restricted in activity for years.

Analysis of Positive Results. Exercise under the standard conditions precipitated attacks of angina pectoris in 34 individuals (7 women and 27 men, Table 6). The amount of exercise necessary

to produce an attack varied in the different individuals. In most instances (22 cases), 20 to 40 trips were necessary. The sequence of events during exercise was uniform. After a certain amount of exercise the patient began to experience discomfort, which was not intense and did not interfere with continuation of the exercise. Frequently, at this time, the patient's expression became anxious and occasionally one hand reached involuntarily toward the sternum. Within 2 to 10 trips after the onset of these symptoms, the discomfort increased rapidly, and suddenly became so intense that the patient was forced to stop. This point was quite definite and was taken as the end point of the test.

The patients always stated that the attacks produced were identical with those experienced in daily life. Observation and questioning of the patient at the time of the attack frequently brought to light details which were unobtainable in the usual clinical history. The distribution and character of the pain could be determined definitely and accurately. The duration of the attack could be measured.

There have been absolutely no untoward effects from the exercise or the induced attacks. Dyspnea was usually quite marked at the onset of the attack, but cyanosis, pallor or flushing were not observed. In a few individuals the pain increased in severity after the exercise had been stopped. These were the only persons who required nitroglycerin to secure relief from the attack. Some individuals experienced headache rather than relief of chest pain after nitroglycerin. In these persons, the attacks were of short duration ($\frac{1}{2}$ to $1\frac{1}{2}$ minutes) and presumably subsided before the nitroglycerin had begun to act, so that only the unpleasant effects of the drug were experienced.

The sudden development of pain, severe enough to cause the patient to stop, the motionless attitude of the patient during the attack, the anxious expression with hands pressed to the sternum and the prompt relief by nitroglycerin when administered gave objective evidence sufficient to establish the diagnosis of angina pectoris in the majority of patients. In other individuals careful questioning during or immediately after the attack was of great aid in establishing the diagnosis. It is hardly conceivable that patients not subject to attacks of angina pectoris should develop such symptoms under the physiologic conditions of this test.

The number of trips necessary to precipitate an attack of angina pectoris gave insight into the frequency of attacks in daily life and indicated the severity of the patient's illness. The intensity of the individual attack varied, however, in different individuals and was not related to the number of trips necessary to induce an attack.

Constancy of Results. In 30 instances the standardized test was repeated one or more times on different days (Tables 2 and 6). The amount of exercise necessary to precipitate an attack of angina was

quite constant for each individual, even though the tests were separated from each other by several months (Table 2). In the analysis of the data the result of the first test was eliminated when it differed markedly from the results of subsequent tests, for, as has been demonstrated above, angina is frequently precipitated more readily at the time of the first test. Of the 30 cases retested, 20 showed a maximum variation of 6 trips in the amount of exercise necessary to precipitate angina pectoris. Four of the remaining 10 cases showed a maximum variation of less than 10 trips, 2 showed checks within 12 trips and the remaining 4 had only 2 tests.

Analysis of Negative Results. Of the 53 patients who performed the test, 19 did not develop angina pectoris when exercising under standard conditions. These patients illustrate the difficulties and dangers in making a diagnosis of angina pectoris on the basis of history alone.

GROUP I. *Patients Who Were Shown to Have No Angina Pectoris.* Six patients developed symptoms on exertion which were identical with those for which they sought medical advice. Observation of these patients during the time that the symptoms persisted enabled us to evaluate their symptomatology more carefully than was previously possible. Four of these patients complained of substernal "choking" on exertion. This was demonstrated to be dyspnea, due to emphysema. This dyspnea gradually developed and gradually increased during the exercise, and subsided slowly thereafter with no precordial element and no radiation. A fifth patient developed sharp sticking pains in the left midaxillary line which persisted less than 1 second and which did not prevent him from continuing the exercise to the point of exhaustion. In the sixth case it was demonstrated that the pain was not related to exertion and was present only when pressure was exerted on the 6th and 7th ribs in the axillary line.

GROUP II. *Patients Who Had Had No Recent Attacks of Angina Pectoris.* Three patients who had clearly defined histories of angina pectoris had not experienced attacks for many months. In none of these individuals were we able to precipitate angina by the exercise tolerance test. One of these individuals had noticed the disappearance of anginal pain following coronary occlusion 2 years previously. Another patient had had 2 attacks of constricting chest pain about 1 year before the test was performed, but since that time he had been entirely free from pain despite the fact that his occupation (peddler) necessitated climbing many flights of stairs every day. The third patient experienced no anginal pain, either spontaneously or induced, during 4 months of observation.

GROUP III. *Patients in Whom the Diagnosis of Angina Pectoris Was Doubtful.* In 9 patients, reevaluation of the case history by independent observers failed to corroborate the diagnosis of angina pectoris. In these patients, the description of the attacks was found

to be atypical. Because of the uncertainty of the diagnosis, 4 cases were admitted to the hospital wards. In these individuals exercise in the cold room and out of doors in cold, windy weather repeatedly failed to precipitate angina. Subcutaneous injections of epinephrin in increasing doses up to 1 cc. of a 1 to 1000 solution failed to precipitate anginal attacks in 3. The fourth patient developed an attack of angina with 1 cc., but not with smaller doses. This patient, on further study, repeatedly revealed concentrations of over 200 mg. of protein in the lumbar spinal fluid and normal concentrations of protein in the cisternal fluid, which suggested that his complaints were due to disease of the central nervous system. The remaining 4 patients were able to exercise to the point of fatigue without developing angina. All 9 patients in this group have been followed for periods varying from 3 to 9 months, without having developed any further evidence of angina pectoris.

GROUP IV. *Patients Who Had Angina But in Whom the Diagnosis Could Not Be Confirmed by the Exercise Tolerance Test.* One patient with hyperthyroidism had developed the typical symptom complex of angina pectoris with the onset of his thyrotoxicosis. Despite a clinical history of angina on both rest and effort, we were unable to precipitate pain by prolonged exertion.

Comment. The standardized exercise tolerance test offers a simple and safe method of precipitating attacks of angina pectoris under controlled conditions duplicating those under which attacks are produced in daily life. The physiological conditions, such as temperature, excitement, food, medication and the influence of recent attacks, which were found to modify the amount of exercise necessary to precipitate angina, have their counterpart in daily life, and are probably in part responsible for the variable histories which these patients give. Further studies may reveal other factors of importance. The relative constancy of the amount of work necessary to produce an attack of angina under standard conditions indicates some fundamental relationship between the amount of work done, the demands upon the heart and the ability of the heart or coronary vessels to meet these demands.

The ability to produce attacks of angina pectoris at will affords a means of diagnosis, evaluation of therapeutics and study of the basic physiology of this condition. The influence of environmental factors has been presented above. The therapeutic benefits of medication and further reports on the effect of total ablation of the thyroid gland will be the subjects of forthcoming communications. Studies are also being carried out on the changes in blood pressure, heart rate, velocity of blood flow, minute volume output of the heart, respiration and oxygen consumption of the body during anginal attacks.

The opportunity to observe the patient during an attack may be

of great aid in establishing the diagnosis. Cases 7 and 28 had been treated for gastro-intestinal disorders for several years. It was possible to demonstrate that the epigastric discomfort of which these patients complained was a clutching sensation which came on only with exertion and radiated in one case to the suprasternal notch and in the other case to the manubrium and down the left arm. Case 23 had been treated for neuritis of the left arm for over a year. Personal observation of this patient during attacks demonstrated that this pain came on with exertion, began in the left wrist and radiated up the inner aspect of the left arm to the substernal region. In several patients whose clinical histories were difficult to evaluate because of language difficulties, the invariable onset of pain with specific amounts of exercise and the radiation typical of angina pectoris established the diagnosis.

Mackenzie¹⁰ has pointed out the difficulties in obtaining a clear description of the intensity and distribution of pain referred from the heart. Observation of the patient while the pain is present may make it possible to obtain an accurate conception of the severity of the discomfort and may enable the observer to outline accurately the distribution and limits of the pain.

The factors precipitating angina pectoris are varied, and because of this, the ability to precipitate angina under the standard conditions of the test cannot be considered pathognomonic of the condition. Attacks of angina may be precipitated not only by exertion but also by emotion, paroxysmal heart action, adrenalin or anoxemia. Attacks may also occur when the patient is at rest or even during sleep. Most patients, however, develop attacks of angina on exertion, even those who also have attacks on excitement or when at rest. The fact that the clinical characteristics of the attacks are identical under a variety of conditions suggests a common underlying mechanism. The study of angina pectoris under the conditions outlined above is of advantage in that the predisposition of the patient to anginal attacks can be measured accurately, and the attacks provoked and studied at will. The inability to induce an attack under conditions duplicating those which cause attacks in daily life, while not proof positive of the absence of this disease, must leave the diagnosis open to question and should lead the examiner to reëvaluate the history carefully. Another more probable basis for the symptoms usually will be found. One of our patients undoubtedly had a compensation neurosis. Two others had sharp sticking pains in the region of the apex, which were not related to exertion and which were probably functional in nature. Reference has already been made to the difficulty in properly evaluating the symptom of "choking," of which many patients with pulmonary disease and early congestive failure complain. The differentiation between the heart pain of congestive

heart disease and true angina pectoris frequently offers difficulties which may be eliminated by the exercise tolerance test.

The relative amount of work required to precipitate attacks of angina pectoris in an individual gives us a means of evaluating the severity of the condition. Thus, Case 29 who could perform approximately 65 trips before angina developed was obviously less seriously incapacitated than Case 1 who could perform only 9 to 11 trips. Finally, the relative constancy of the amount of work required under standardized conditions to precipitate attacks in the individual patient enables one to evaluate the patient's condition from time to time regardless of season or climate and offers an objective criterion for evaluating the effect of therapy.

Summary. 1. A simple and safe standardized exercise tolerance test is described for use in patients with angina pectoris.

2. The results of the test in a group of 57 consecutive patients with the clinical diagnosis of angina pectoris are presented.

3. Exercise performed under the standard conditions of the test induced attacks in 34 patients. These attacks were precisely like those experienced in daily life.

4. When the standardized test was repeated, even months later, the same amount of exercise again precipitated an attack in the same individual.

5. Nineteen patients did not develop an attack under the standardized conditions. The diagnosis of angina pectoris eventually proved to be exceedingly doubtful in all but one of these patients.

6. Objective evidence is presented illustrating the influence of various environmental factors on the amount of exercise necessary to precipitate attacks of angina pectoris in patients with this condition.

7. The test affords a means of investigating angina pectoris and is of distinct value as an aid in diagnosing doubtful cases and in evaluating both the condition of the patient and the results of therapy.

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WHAT TREATMENT IN EARLY SYPHILIS ACCOMPLISHES.†

I. RELAPSE AND "CURATIVE" RESULTS.

BY JOHN H. STOKES, M.D., with LIDA J. USILTON, M.A.,* and HAROLD N. COLE, M.D., JOSEPH EARLE MOORE, M.D., PAUL A. O'LEARY, M.D., UDO J. WILE, M.D., THOMAS PARRAN, JR., M.D.,* JOHN McMULLEN, M.D.*

FROM any material on early syphilis it is highly desirable to secure a forward-looking glimpse into the ultimate outcome of treatment for syphilis as it concerns the individual patient. The previous studies of early syphilis¹ have indicated certain landmarks of procedure and have quite clearly demonstrated the agents and methods for the control of infectiousness. The difficulties of follow-up in clinic patients and the time required to collect so large a material, as has been pointed out, rapidly reduce the mass of material available for study with each month and year elapsed since the onset of the infection. Of the original 6807 cases with diagnosed early syphilis on admission, there remain 1360 patients who were under treatment or observation for 2 years or longer; 5 to 10 years after infection there remain only 295 cases on whom even an approximation to ultimate outcomes can be discussed; and of cases observed for 15 years, a mere thimbleful of 14 cases. The discussion here presented, then, cannot be accepted as that of true end results of modern treatment. Rather it is a sampling for trends in the effort to see what, if anything, we are accomplishing and whether or not it is worth while. Moreover, it is necessary to realize that the 1360 cases forming the material of this study have not been on a 2-year probationary period since the cessation of treatment. Treatment in many cases has been continued through a part or all of the 2-year period. Had the study been restricted to patients who had had 2 years' probation following the cessation of all treatment, the material would through shrinkage have lost much of its statistical usefulness.

The purpose of this study, then, is to analyze the course of treated early syphilis through a period of 2 years or longer, as distinguished from the larger previously studied group, observed for only 6 months or longer. It is hoped that such a study will begin to indicate in what ways and to what degree treatment is worth while for the

* Names with asterisk represent the U. S. Public Health Service; names without asterisk represent the Coöperative Clinical Group.

† This and the two following studies were conducted by the coöperation of the syphilis clinics of the University of Pennsylvania, Western Reserve University, the Johns Hopkins University, The Mayo Clinic, the University of Michigan, assisted by the U. S. Public Health Service and supported by a special fund contributed by an anonymous donor and a grant by the Milbank Memorial Fund.

individual patient; and whether, with a given period and amount of treatment, something approaching a standard result can be obtained. Such a definition of outcome and procedure would enable the physician to speak in much more definite terms to himself and to his patient. It would reduce, and subsequent studies might ultimately do away with, the always present uncertainty as to when to stop; and if no endpoint could be determined, a comparison of the outcome of treated and untreated cases might furnish a basis for demonstrating the worthwhileness or the relative futility of modern treatment as regards the individual outcome. (See subsequent paper.) Insofar as the material in early syphilis permits, such comparisons have been made. Inevitably the tone of such a presentation will be more speculative than the preceding studies on early syphilis by the Coöperative Clinical Group; for in the last analysis, we are not dealing with time periods which permit of assertion, or with material so controlled that speculation can be eliminated. Judicious theorization may none the less serve the purposes of constructive future observation and thought.

This paper will also include, by way of catching up certain loose threads in previous studies, a survey of the total early syphilis material of 6807 cases from the standpoint of all types of relapse. This will meet the objection that previous estimates of relapse were based on a 6 months' material in which a very considerable proportion of patients had presumably entered and passed through the period of greatest frequency of relapse and dropped from observation before they could be included in the 6 months' observation series.

In order to determine whether the 2-year observation material and the conclusions derived from it can be regarded as fairly representative of what may be expected of early syphilis as a whole, as influenced by the stage of infection on beginning treatment, the proportions of seronegative and seropositive primary, early secondary and delayed secondary syphilis in the total cases diagnosed as early syphilis were compared with the proportions in the 2-year observation group. The practical identity of the proportions in the two groups indicates that the 2-year cases are a fair sample of the whole group of early syphilis, and that expectancy and results based on the 2-year group may properly be regarded as applicable to early syphilis in its entirety, if the early syphilis patient will persist in treatment and observation for 2 or more years.

Cases of Early Syphilis Under Observation-Treatment for any Period of Time. *Frequency of All Forms of Relapse.* In Table 1, all forms of relapse are considered in terms of the stage of the disease at which the patient began treatment. The total incidence of relapse, 10.1%, is lower than in the cases observed for 6 months or longer (19.7%). The explanation for the disparity lies in the fact that nearly half the material included in the total diagnosed

was observed so short a time that no opportunity to observe the maximum incidence of relapse was provided. The figures in previous studies, therefore, better represent the incidence of early relapse.

TABLE 1.—COMPARATIVE INCIDENCE OF RELAPSE IN PATIENTS WITH EARLY SYPHILIS TREATED OR OBSERVED FOR 6 MONTHS OR LONGER WITH THOSE FOR ANY PERIOD OF TIME.

Type of relapse.	Seronegative primary.		Seropositive primary.		Early secondary.		Delayed secondary.		Total.	
	Total cases treated.	Six months or more.	Total cases treated.	Six months or more.	Total cases treated.	Six months or more.	Total cases treated.	Six months or more.	Total cases treated.	Six months or more.
<i>Number.</i>										
Early infectious:										
Mucocutaneous . . .	59	56	125	118	220	214	7	6	411	394
Ocular	2	2	12	11	32	28	46	41
Central nervous system:										
Symptomatic . . .	10	9	35	33	103	89	1	1	149	132
Asymptomatic . . .	13	12	20	13	83	77	8	8	124	110
Benign, late	3	3	10	10	36	36	1	1	50	50
Cardiovascular	3	3	3	3	24	24	30	30
Visceral	2	2	2	2
Total cases relapsing*	78	74	176	159	417	392	16	15	688	640
Total cases	709	342	1319	585	4640	2252	139	65	6807	3244
<i>Per cent.</i>										
Early infectious:										
Mucocutaneous . . .	8.3	16.4	9.5	20.2	4.7	9.5	5.0	9.2	6.0	12.1
Ocular	0.3	0.6	0.9	1.9	0.7	1.2	0.7	1.3
Central nervous system:										
Symptomatic . . .	1.4	2.6	2.7	5.6	2.2	4.0	0.7	1.5	2.2	4.1
Asymptomatic . . .	1.8	3.5	1.5	2.2	1.8	3.4	5.8	12.3	1.8	3.4
Benign, late	0.4	0.9	0.8	1.7	0.8	1.6	0.7	1.5	0.7	1.5
Cardiovascular	0.4	0.9	0.2	0.5	0.5	1.1	0.4	0.9
Visceral	0.04	0.09	0.03	0.06
Total cases relapsing .	11.0	21.6	13.3	27.2	9.0	17.4	11.5	23.1	10.1	19.7

* Each relapse is recorded, although some cases have 2 or more.

As regards the individual forms of relapse, the comparative figures are: Mucocutaneous, total diagnosed group, 6%; 6 months' observation group, 12.1%; asymptomatic neurosyphilis, 1.8% *vs.* 3.4%; symptomatic neurosyphilis, 2.2% *vs.* 4.1%; cardiovascular, 0.4 *vs.* 0.9%.

The patient who begins treatment in the seropositive primary stage of syphilis has the highest incidence of mucocutaneous relapse. Why is this so? Because he has had to combat an already entrenched (Wassermann positive) infection, with no other aid than

that of treatment, lacking the immunizing or protective effect of his general secondary reaction. The patient with seronegative primary syphilis finds himself with an untrenched infection, compelled to rely entirely on the effect of treatment. He achieves an advantage by the "untrenchment," a disadvantage in the form of increased frequency of mucocutaneous relapse by the lack of systemic reaction, which brings him out midway between the patient with seropositive primary syphilis and the patient who has had florid secondaries. Thus it appears that so far as mucocutaneous relapse is concerned, the most vulnerable position a patient can hold is that of a seropositive primary case. His skin and mucous membranes will, so to speak, be inspired to, but will not achieve full protective reaction. He will have a tendency, an exaggerated tendency, to relapse.

If such a group of considerations could be found to apply to all forms of relapse, and to the outcome of the disease, it would furnish justification from the standpoint of the individual for allowing all patients with early syphilis to go on to secondaries, build up their immunity reactions and thenceforth combine the immunity with the effects of treatment. This point is further discussed in connection with the effect at various stages of various systems of treatment. Rejection of such delay as a treatment policy must rest on the social consideration of the control of infectiousness in the large body of patients with early syphilis and on the fact that there is at least a slight advantage with reference to all other forms of relapse, in beginning treatment while the chancre is still seronegative. With reference to the seropositive chancre stage, the treatment outcomes, presently discussed, indicate that for the individual there may be a slight advantage in permitting him to go on to secondaries if continuous treatment is available.

When, however, the advantage of cutting off infectiousness in almost all patients with early syphilis as soon as they are seen is weighed against the costs, risks and some uncertainty attached to the immunizing process of developing secondaries in quarantine, there can be little doubt that immediate treatment of the early case, the earlier the better, is the socially wise policy, and one not productive of new and significantly increased dangers for the individual. But the physician must warn the seropositive primary patient that he must be doubly vigilant with regard to relapse, and, if anything, even more persistent in treatment than the patient who has developed secondaries. The treatment optimums on which this statement is based are presently discussed.

The Effect of the Amount of Treatment on Incidence of Relapse. In the new study (Table 2), it appears that there is a steady drop in the incidence of all forms of relapse with an increasing number of arsphenamin injections, except in the case of asymptomatic neurosyphilis and cardiovascular syphilis. Both these latter increased

in frequency (1.2% to 5.3% and 0.3% to 2.1%, respectively) as treatment increased. Whether or not this increase is to be entirely attributed to the presumption that more treatment will be given to patients showing signs of increased resistance or threatened complications or not—will be considered in connection with the 2-year results of treatment.

TABLE 2.—FREQUENCY OF RELAPSE IN PATIENTS TREATED AND OBSERVED IN THE EARLY STAGES OF SYPHILIS FOR ANY PERIOD OF TIME.

Type of relapse.	Amount of arsphenamin.					
	9 doses or less.	10 to 19 doses.	20 to 29 doses.	30 to 39 doses.	40 doses or over.	Total.
			Number.			
Early infectious:						
Mucocutaneous	314	66	27	3	1	411
Ocular	40	4	2	46
Central nervous system:						
Symptomatic	105	26	12	4	2	149
Asymptomatic	51	42	19	7	5	124
Benign, late	29	18	2	1	..	50
Cardiovascular	14	6	5	5	..	30
Visceral	2	2
Total cases relapsing . .	473	147	64	20	8	712*
Total cases	4094	1645	754	244	94	6831*
			Per cent.			
Early infectious:						
Mucocutaneous	7.7	4.0	3.6	1.2	1.1	6.0
Ocular	1.0	0.2	0.3	0.7
Central nervous system:						
Symptomatic	2.6	1.6	1.6	1.6	2.1	2.2
Asymptomatic	1.2	2.6	2.5	2.9	5.3	1.8
Benign, late	0.7	1.1	0.3	0.4	..	0.7
Cardiovascular	0.3	0.4	0.7	2.1	..	0.4
Visceral	0.05	0.02
Total cases relapsing . .	11.6*	8.9	8.5	8.2	8.5	10.4
Total cases	100.0	100.0	100.0	100.0	100.0	100.0

* There were 24 cases having 2 relapses which fell in different treatment groups. The relapses were included in both places and, therefore, raised the totals in the total cases from 6807 to 6831 and 688 to 712.

Cases of Early Syphilis Under Treatment-Observation for 2 Years or More. *Results of Treatment-Observation.* "Satisfactory results" as here used includes all cases classified as "cured," with or without physical examination, probation, or reinfection, and those cases which had a "satisfactory result" although heavy metal therapy was continued long after this had been obtained. A "satisfactory

result" indicates a long series of negative blood serologic tests, in many cases a negative spinal fluid, no recent clinical or serologic signs of relapse or progression, and in most instances a negative physical examination.

In the series observed for 6 months or longer, 3244 cases, the "satisfactory results," using the criteria indicated above, reached 27.9%; in the 2-year or longer series, 1360 cases; this had increased to 52.7%. The increased proportion is probably due (1) to longer treatment in the better observed patients, or (2) to the fact that as time passes the tendency to relapse automatically declines and the disease is brought to a standstill. This proportion of arrest is compared in a subsequent paper with that to be expected of untreated cases as disclosed by Bruusgaard's study of Boeck's material.

Effect of Treatment Systems on the Proportion of Satisfactory Results. Let it be recalled that the proportions just given from Table 3 represent the aggregate of all methods of treatment: continuous, intermittent, irregular and intensive.* From Table 3 it now appears that, classified on the basis of the system of treatment employed and the stage of the disease in which treatment is begun, a consistent group of differences in results begins to appear. The 2-year satisfactory results in seropositive primary syphilis are consistently poorer than those obtained in seronegative primary syphilis regardless of system, and likewise poorer than in fully developed secondary syphilis *treated by a continuous system*. The results in secondary syphilis under intermittent, irregular and intensive treatment are, on the contrary, inferior even to those in seropositive primary syphilis. The lead of seronegative primary syphilis is, indeed, a notable one, and represents the best that modern methods have to offer—86.4% satisfactory results if treatment is continuously given to an infection identified by dark field before the blood test becomes positive. Once the blood test becomes positive, the proportion drops to 64.3%, even with continuous

* *Continuous treatment* is defined as uninterrupted treatment with an arsphenamin or a heavy metal, or both, whether administered in alternation or simultaneously, throughout treatment, including so-called "overlapping" treatment. The distinctive feature of this scheme is its *uninterrupted* character. In this group were included patients receiving prolonged treatment, even though its continuity was broken toward the last by a lapse.

Intermittent treatment is defined as treatment with an arsphenamin or heavy metal, or both, which is interrupted by short rest intervals throughout treatment, whether they are purposeful or not. The distinctive feature is the rest interval of 1 month or more duration.

Irregular treatment is defined as treatment with an arsphenamin or heavy metal, or both, which is absolutely irregular, no one of the systems heretofore described being consistently or even approximately followed.

Intensive treatment is defined as treatment with an arsphenamin or heavy metal, or both, which consists of short, intensive arsphenamin phases (3 to 4 injections in 3 to 8 days), alternating with a more or less prolonged heavy metal course of mercurial inunctions or intramuscular injections of mercury or bismuth (4 to 8 weeks or more) with purposeful rest intervals. (Ven. Dis. Inform., Washington, 13, 209, 1932.)

treatment; but it rises again to only a little short of the seronegative group result, that is, to 81.5%, when the patient with secondaries is continuously treated.

TABLE 3.—CASES OF EARLY SYPHILIS TREATED OR OBSERVED FOR 2 YEARS OR MORE, SHOWING THE RESULT OF TREATMENT BY DIAGNOSIS ON ADMISSION AND THE SCHEME OF TREATMENT EMPLOYED.

Scheme of treatment.	Seronegative primary.		Seropositive primary.		Early secondaries.		Delayed secondaries.		Total.	
	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.
					<i>Number.</i>					
Continuous	19	3	18	10	97	22	3	..	137	35
Intermittent	47	10	85	37	245	155	10	6	387	208
Irregular	29	24	41	78	108	252	4	10	182	364
Intensive	5	3	2	3	4	29	..	1	11	36
Total	100	40	146	128	454	458	17	17	717	643
					<i>Per cent.</i>					
Continuous	86.4	13.6	64.3	35.7	81.5	18.5	100.0	..	79.7	20.3
Intermittent	82.5	17.5	69.7	30.3	61.3	38.7	62.5	37.5	65.0	35.0
Irregular	54.7	45.3	34.5	65.5	30.0	70.0	28.6	71.4	33.3	66.7
Intensive	62.5	37.5	40.0	60.0	12.1	87.9	..	100.0	23.4	76.6
Total	71.4	28.6	53.3	46.7	49.8	50.2	50.0	50.0	52.7	47.3

* "Satisfactory results" includes all cases classified as cured, with or without a physical examination, probation or reinfection, and those cases which apparently had a satisfactory result although heavy metal treatment was continued long after one had been obtained (especially referable to Western Reserve cases).

It is unnecessary here to comment again on the further demonstration afforded by these figures, of the worth of continuous treatment and the progressively increasing ineffectiveness of the intensive and the irregular types of treatment. This has been supported by previous studies, and here merely receives confirmation. Without further discussion, then, a possible explanation for the differences in effect of treatment of all types in the seronegative and seropositive primary stages and of continuous treatment in the secondary stage may be sought.

First of all, it is apparent that treatment of any kind has an exceptional effect if applied in the seronegative primary stage. Seronegative primary syphilis in man must, indeed, be a rather easily responsive infection, relatively speaking, if totally irregular treatment can produce 54.7% satisfactory results. Bruusgaard finds the proportion of spontaneous cures to approximate 43%, so

that even irregular treatment increases the natural advantage of the bodily defense. The first element to be invoked, then, in a possible explanation of the observed variations in treatment effect at different stages, is that of intrenchment of the infection. The seronegative primary syphilis case responds readily to anything or almost nothing because the spirillicides and artificial stimulation of resistance by medication overwhelm the organism, still exposed and unadjusted to its new environment and unprotected from assault by fibroid tissue reaction. The seropositive primary case has lost this advantage of an exposed organism. It has not gained, in exchange, the advantage of its own constitutional reaction against the disease by the development of visible secondaries.

But if it is so much of an advantage theoretically to allow the patient to develop a constitutional and especially a cutaneous reaction to his infection, why is not this advantage manifest in the results of other forms of treatment than the continuous in the secondary stage? In explaining the discrepancy between continuous treatment results, on the one hand, and intermittent, irregular and intensive treatment, on the other, in secondary syphilis, the rest interval may again be invoked as the primary difference between the two groups, and the probable explanation of the greater effect of continuous treatment. This explanation would be satisfying on sight were it not for another observed discrepancy in Table 3. The effect of intermittent treatment in seropositive primary syphilis is slightly better than is that of continuous treatment. How can such an unexpected effect be explained?

It is conceivable that the biologic course of resistance development in syphilis will account for both phenomena. In seronegative primary syphilis the full effect of treatment is exerted upon the organism; the patient is cured by spirillicidal action, so to speak; during the early period of treatment, when in all probability the most significant blows are struck, his spontaneously developed resistance based on the presence of the organism plays little part. The proportion of satisfactory results, therefore, varies with the intensity and duration of application of the spirillicides; and since this is at its maximum with continuous treatment, and at its least with irregular treatment, the results vary accordingly. On the other hand, the patient once being in process of constitutional reaction to his infection, but short of its consummation, especially in the cutaneous phase, as he is in seropositive primary syphilis, every pause in treatment, every cessation of spirillicidal action permits, in theory, a revival of organisms and a new, if brief, stimulus to systemic reaction against the disease. Thus it may come about that intermittent treatment, with its pauses, permits the adding of some, even if small, increments of constitutional reaction and resistance to the effects of treatment. The ultimate outcome of spirillicide plus fractional resistance increments in rest

periods at this stage is a little better than if the patient had been obliged by a continuous system of treatment to fight his infection solely by spirillicidal means, introduced from without. Hence we witness, at a stage when bodily reaction, as indicated by serologic positiveness, has reached the point where it can add its effect to treatment, the curious paradox of an inferior method of treatment from the spirillicidal standpoint, producing superior ultimate results because its rest periods permit the addition to the patient's resources of some bodily resistance following revivals of the infection.

How shall such a group of considerations be applied to the equally curious situation of the patient with full cutaneous secondary reaction, who, if continuously treated, achieves a result almost equal to that obtainable in seronegative primary syphilis but falls to the lowest level of all in ultimate results if rest intervals are permitted at this stage, as in intermittent, intensive or irregular treatment? Here it may be presumed that the patient with secondaries has added the full force of his bodily reaction to the possibilities of whatever form of treatment he is given. Rest periods no longer mean for him increments of resistance, as they may in the seropositive primary patient who has not yet achieved his full cutaneous reaction. The effect of the method of treatment as such, therefore, again asserts itself, augmented by resistance factors but offset by tissue intrenchment of the organism in healing local tissue foci. Then, as in other aspects of early syphilis, including seronegative primary and the first 4 years of latency (Moore), continuous treatment asserts its primacy.

It is realized that an explanation involving so many incompletely explored areas as the concept of constitutional resistance to syphilis is not ready for standardized application in practice, particularly in the treatment of seropositive primary syphilis. Further observation and thought on the effect of a staggered or fractional resistance development as a substitute for postponement of treatment until secondaries appear is, however, justified as a possible future method of dealing with seropositive primary syphilis.

Conclusions. 1. The maximum frequency of relapse in early syphilis under observation and treatment 6 months or longer is 19.7% (mucocutaneous, 12.1%; asymptomatic neurosyphilis, 3.4%; symptomatic neurosyphilis, 4.1%; cardiovascular, 0.9%).

2. The incidence of mucocutaneous relapse is lowest in those patients who have had a full secondary reaction to the disease.

3. Patients who begin treatment in the seropositive primary stage have the highest incidence of mucocutaneous relapse.

4. Nonetheless, no advantage appears on other grounds in permitting a seropositive primary case to go on to secondaries.

5. The seropositive primary case must be treated with exceptional thoroughness.

6. Relapse decreases in frequency with an increasing number of

arsphenamin injections, except in the case of cardiovascular and asymptomatic neurosyphilis.

7. Satisfactory ("curative") treatment results are obtained in cases observed 2 years or longer (up to 20 years) in 52.7% of cases without respect to amounts and methods of treatment.

8. Treatment begun in seronegative primary syphilis (dark field diagnosis) by a "continuous" system yields 86.4% "satisfactory results."

9. The proportion of "satisfactory results" drops to 64.3% by the same method if the treatment is delayed until the serologic tests become positive.

10. If the patient has developed secondaries, the proportion of "satisfactory results" (2 years and after) again rises to 81.5% by a continuous system of treatment.

11. Other systems of treatment do not yield as satisfactory results. But in seronegative primary syphilis even irregular treatment yields 54.7% "satisfactory results."

12. The observed differences in treatment by various methods are discussed in terms of a theory of the function of resistance and the rest interval.

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WHAT TREATMENT IN EARLY SYPHILIS ACCOMPLISHES.

II. OPTIMUM TREATMENT.

By JOHN H. STOKES, M.D., with LIDA J. USILTON, M.A.,* and HAROLD N. COLE, M.D., JOSEPH EARLE MOORE, M.D., PAUL A. O'LEARY, M.D., UDO J. WILE, M.D., THOMAS PARRAN, JR., M.D.,* JOHN McMULLEN, M.D.*

IN Paper I, case material of 1360 patients with early syphilis treated and observed for from 2 to 20 years was discussed from the standpoint of relapse and satisfactory or "curative" results. The difference in behavior of various phases of early syphilis and the results obtained by the scheme of treatment (continuous, *i. e.*, without rest intervals) producing the highest proportion of "cures" were discussed. The present paper takes up the definition of the amount of treatment required in various phases of early syphilis, the effect of arsphenamin dosage and of spinal fluid abnormality on

* Names with asterisk represent U. S. Public Health Service; names without asterisk represent the Coöperative Clinical Group.

outcome and the irreducible margin of failure with the methods of treatment employed in this series.

Optimum Amounts of Treatment. *Influence of the Number of Injections of Arsphenamin on Satisfactory Results.* It appears that the highest proportion (85%) of satisfactory results in seronegative primary syphilis is obtained in the group receiving 10 to 19 arsphenamin injections with accompanying heavy metal; in seropositive primary syphilis it requires 25 to 35 injections to produce the highest proportion of good results obtainable, namely, 65%. In early secondary syphilis, the highest proportion of good results is achieved by 20 to 29 injections (58%). In viewing the downward trend of good results as secondary syphilis develops it must be recalled that we are dealing in this table with all systems of treatment, and that intermittent and irregular schemes of treatment in secondary syphilis give the relatively poor showings which bring the proportion of good results down to 58%.

TABLE 4.—EARLY SYPHILIS TREATED OR OBSERVED FOR 2 OR MORE YEARS, SHOWING THE RESULT OF TREATMENT BY THE STAGE OF THE DISEASE AND THE AMOUNT OF ARSPHENAMIN ADMINISTERED.

Amount of arsphenamin.†	Seronegative primary.		Seropositive primary.		Early secondaries.		Delayed secondaries.		Total.	
	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.	Satisfactory results.*	All other outcomes.
Little or no arsphenamin or heavy metal					<i>Number.</i>					
9 doses or less	13	1	3	6	1	3	4	10
10 to 19	39	7	49	46	54	56	4	1	81	85
20 to 29	33	11	54	28	138	147	6	10	232	210
30 to 39	10	5	16	9	166	120	5	3	258	162
40 or over	5	9	12	18	67	71	1	1	94	86
Little or no arsphenamin and much heavy metal	2	..	23	54	1	1	41	82
Total	100	40	146	128	454	458	17	17	717	643
Little or no arsphenamin or heavy metal					<i>Per Cent.</i>					
9 doses or less	65.0	35.0	33.3	66.7	25.0	75.0	28.6	71.4
10 to 19	84.8	15.2	51.6	48.4	49.1	50.9	80.0	20.0	48.8	51.2
20 to 29	75.0	25.0	65.9	34.1	58.0	42.0	37.5	62.5	52.5	47.5
30 to 39	66.7	33.3	64.0	36.0	48.6	51.4	50.0	50.0	52.2	47.8
40 or over	35.7	64.3	40.0	60.0	29.9	70.1	50.0	50.0	33.3	66.7
Little or no arsphenamin and much heavy metal	100.0	..	41.7	58.3	..	100.0	46.7	53.3
Total	71.4	28.6	53.3	46.7	49.8	50.2	50.0	50.0	52.7	47.3

* "Satisfactory results" includes all cases classified as cured, with or without a physical examination, probation or reinfection, and those cases which apparently had a satisfactory result although heavy metal treatment was continued long after one had been obtained (especially referable to Western Reserve cases).

† Number of injections of arsphenamin used as the measure of treatment, practically all cases were treated with accompanying heavy metal.

Table 4 presents a series of very interesting aggregates. Relating the number of arsphenamin injections to the stage of the disease at which treatment was begun, the point observed in previous studies, it again appears that the higher number of injections apparently leads to a smaller proportion of satisfactory results than some of the smaller amounts of treatment. Table 5, subsequently discussed, goes far to show that the reason patients receiving the larger number of injections get less satisfactory results is because their infections have in their course shown evidence of unusual resistance, and they have accordingly been given more treatment in the effort to overcome the resistance.

It is apparent again that the seropositive primary stage is the more resistant and requires a larger amount of treatment for the achievement of the best possible results than does seronegative primary syphilis. A greater tendency to relapse or to show various other signs of resistance demands of the patient greater persistence in treatment and a larger total amount of treatment, although with this increased treatment better results are obtained than with similar amounts after syphilis has reached the secondary stage.

That the numbers of injections, regardless of system, given as optimums in the previous paragraph, are not to be regarded as inflexible or universally applicable routine, appears from the analysis of Table 5. From this table it may be seen that even inadequately treated syphilis (less than 20 injections of arsphenamin with heavy metal) yields its proportion of satisfactory results (66%) in patients who were treated for 2 years and never subsequently, yet never received in all more than 20 doses of arsphenamin. The adequately treated patients (more than 20 injections of arsphenamin with heavy metal in the same period) gained only 11% by the adequacy of their treatment. The sharp drawing of the line between adequacy and inadequacy at 20 arsphenamin injections, of course, increases the good results under "inadequate treatment," for Table 4 shows that at least the seronegative primary cases attain their highest proportion of good results from 10 to 19 injections.

As soon as our material is divided into two groups, one in which treatment was suspended at the end of 2 years, and the other in which treatment was continued after 2 years, the analysis of the clinical behavior of each group indicates that those treated for the longer time *did* show clinical and serologic evidence of greater resistance. Even in the adequately treated cases treated after the second year it appears that serologic relapse occurs in 12.6% as against 6% in those whose treatment was not carried beyond the second year. Irreversible Wassermann reactions were present in those treated beyond the second year in 7%, while in those not treated beyond the second year they were present in only 1.7%. The same proportion holds true for neurorelapse and resistant asymptomatic neurosyphilis. It is presumed that patients were

continued on treatment beyond the second year because they showed clinical or serologic signs of resistant infections. The only method of examining the validity of this presumption, possible in this study, which would tend to show that the excessive treatment had a share in producing the resistance of the infection and the lower proportion of good results with the higher number of arsphenamin injections, would be by way of an analysis of the effect of arsphenamin

TABLE 5.—FINAL RESULTS OBTAINED IN EARLY SYPHILIS WITH A COMPARISON OF THOSE ADEQUATELY AND INADEQUATELY TREATED DURING THE FIRST 2 YEARS OF THE INFECTION.

Final results of treatment.	Treatment given during the first 2 years of infection.							
	Adequate.*				Inadequate.*			
	No subsequent treatment.		Subsequent treatment.		No subsequent treatment.		Subsequent treatment.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Grand total, all outcomes	232	100.0	301	100.0	198	100.0	629	100.0
Satisfactory outcome	179	77.2	148	49.2	131	66.2	259	41.2
All other outcomes	53	22.8	153	50.8	67	33.8	370	58.8
Improving when last seen	25	10.8	73	24.3	22	11.1	152	24.2
Relapse: Serologic	14	6.0	38	12.6	20	10.1	86	13.7
Clinical	5	2.2	9	3.0	7	3.5	31	4.9
Irreversible blood	4	1.7	21	7.0	16	8.1	94	14.9
Neurosyphilis	4	1.7	22	7.3	8	4.0	41	6.5
Spinal fluid fast	1	0.4	9	3.0	1	0.5	10	1.6
Dead	5	2.2	3	1.0	4	2.0	5	0.8

* Adequate treatment consists of 20 or more doses of an arsphenamin with accompanying heavy metal; inadequate treatment less than this amount.

TABLE 6.—EFFECTIVENESS OF SIZE OF DOSE OF OLD ARSPHENAMIN IN PATIENTS FOLLOWED FOR 2 YEARS OR MORE, WHO RECEIVED 20 OR MORE DOSES OF ARSPHENAMIN WITH PROPORTIONATE AMOUNT OF HEAVY METAL.

Scheme of treatment.	Total cases.		Satisfactory outcome.		Improved.		Unsatisfactory outcome.		Relapse or resistant serum.		Clinical relapse.		Neurosyphilis, CSF fast.		Dead.	
									Size of dose.*							
	Small.	Large.	Small.	Large.	Small.	Large.	Small.	Large.	Small.	Large.	Small.	Large.	Small.	Large.	Small.	Large.
Continuous	66	25	55	24	1	..	6	Number.	5	..	4	4	1
Intermittent	157	95	94	55	38	23	24	16	19	11	4	3	13	3	1	1
Irregular	109	73	42	16	31	27	34	30	24	25	5	4	17	7	2	..
Total	332	193	191	95	70	50	64	46	48	36	13	7	30	10	7	2
Continuous	100	100	83.3	96.0	1.5	..	9.1	Per cent.	7.6	..	6.1	6.1	4.0
Intermittent	100	100	59.9	57.9	24.2	24.2	15.3	16.8	12.1	11.6	2.5	3.2	8.3	3.2	0.6	1.1
Irregular	100	100	38.5	21.9	28.4	37.0	31.2	41.1	22.0	34.2	4.6	5.5	15.6	9.6	1.8	..
Total	100	100	57.5	49.2	21.1	25.9	19.3	23.8	14.5	18.7	3.9	3.6	9.0	5.2	2.1	1.0

* Size of dose: Males: small, 0.2 to 0.45; large, 0.45 or over. Females: small, 0.2 to 0.3; large, 0.3 or over.

min dosage on outcome. If it can be shown that a higher proportion of good results attends the use of the lower doses of arsphenamin as against the higher, a counterpresumption may be established that at least a part of the less favorable results in the higher-number series is attributable to overuse of the drugs rather than merely to virulence of the disease. This question is examined in Table 6.

In examining the effect of arsphenamin dosage (restricted to "606") on the relatively less favorable outcomes of patients who received the longer series of injections (over 20) the scale of dosage rated as "small" (Table 6) is from 0.2 to less than 0.45 gm. for males and 0.2 to less than 0.3 gm. for females. "Large dosage" is 0.45 gm. or over for men and 0.3 gm. or over for women. On the basis of such a partition, not wholly satisfactory, to be sure, with so small a sample, and the disregard of body weight, on which there were only limited data in this series of cases, it appears that *there is nothing to indicate that large dosage causes any type of unfavorable outcome* when either continuous or intermittent treatment is used. On the other hand, *there is distinct evidence that small dosage has definite shortcomings*. With continuous treatment there is not a single unsatisfactory outcome (deaths not due to syphilis or treatment) on the higher dosage scale. But on the lower dosage scale, 7.6% relapsed or were resistant serologically; 6% had clinical relapses; none had neurosyphilis on either scale. Intermittent treatment shows practically no difference between the dosage scales, except in the matter of neurosyphilis in which the lower dosage scale showed 8.3% as against 3.2% for the higher dosage scale. *These findings not only point out the need for the higher dosage scale, but explicitly negate the idea that arsphenamin as such predisposes to neurosyphilis*. It will be noted that the apparent advantage of the smaller dosage when treatment is irregularly given is confined to a lower per cent of relapse or resistant serologic findings. Even with the irregular treatment scheme the more significant type of unsatisfactory outcome, that of neurosyphilitic involvement, is higher with the small than with the large dosage scale.

We may say, then, that the apparent reduction in good results with prolongation of treatment is not due to the unfavorable effect of a prolonged use of arsenicals. In fact, the evidence points to the desirability of a higher scale of dosage of these drugs than some employed at the present day, at least within the field of the treatment techniques used in early syphilis by the coöperating clinics, in which courses of heavy metal alternate with the arsenical.

Effect of Spinal Fluid Abnormality on Treatment Outcome. Many groups of reported results of treatment for syphilis are notably deficient in that there was no satisfactory control of the spinal fluid. In this series, spinal fluid control was exercised in 1090 patients, or 80%, of the 1360 patients under observation or treatment for 2 years or more. Of the 1090 patients, 33% (365) showed some degree of spinal fluid abnormality. The base line was 65% of

satisfactory results when the spinal fluid was negative. When the cell count was 6 or over, and all other findings negative, the satisfactory results in this group dropped to 62%. When the cell count was 5 or over and protein was increased but the Wassermann and colloidal tests were negative, the satisfactory results dropped to 35%. When the cell counts and Wassermann test were positive and the protein and colloidal tests positive or negative, the proportion of satisfactory results under all varieties of treatment aggregates only 28%; and in cases with a definitely abnormal spinal fluid classified as Group III (paretic formula) only 9% of such patients obtained a satisfactory result. Analyzed with respect to the influence of treatment method on result in these cases, it was found that irregular treatment was the principal factor in causing an abnormal spinal fluid.

Regardless of the perplexities introduced into the question of optimums in Table 4, it is impossible to escape the clearness of the demonstration which it affords; that *adequate treatment for early syphilis within the first 2 years, in each and every category of course and outcome, yields substantially better results than does inadequate treatment, by whatever method. More than 20 arsphenamin injections is better than less than 20 arsphenamin injections, each with the accompanying heavy metal.*

Moreover, it further deserves emphasis, that there is no deadline drawn at 2 years for the patient who has received inadequate treatment within that period. Even granted that he does not achieve a satisfactory result within this ideal period, it is worthwhile to go on. Table 7 expressly examines this question, with the following results. Of those patients who had had inadequate treatment within the first 2 years of their infection (less than 20 arsphenamin injections with the accompanying heavy metal), 33% will ultimately become symptom-free and serologically negative with further treatment. What form shall this further treatment take? It is notable that it should not be merely a continuation of heavy metal therapy, *but a further administration of the arsphenamin.* If heavy metal alone was given, only 18% of the patients so treated were reclaimed. If 10 or less injections of an arsphenamin were also given, 24% were reclaimed. If *more than 10 injections of an arsphenamin were given in conjunction with the continued heavy metal*, 50% of the unsatisfactory results were brought to a serologic and clinical negativity. In the categories of serologic and neurorelapse following inadequate treatment, this statement was borne out. The group of patients adequately treated during the first 2 years tends to bear out the same contention, though in much less striking fashion. Representing possibly an even higher degree of resistance which probably led to their better adherence to treatment schedule, they became symptom-free after the first 2 years by the continued use of heavy metal in 30% of cases. If more than 10 injections of an arsphenamin were added,

the proportion was raised to 58%. *The resistant patient with early syphilis should, then, be treated not with heavy metal alone, but with heavy metal plus 10 or more injections of an arsphenamin in addition to those which he received in the 2-year period.*

TABLE 7.—TYPE OF UNSATISFACTORY OUTCOME AT THE END OF THE FIRST 2 YEARS OF TREATMENT OF EARLY SYPHILIS WITH THE PATIENT'S RESPONSE TO FURTHER TREATMENT.

Cases having an unsatisfactory result at end of first 2 years, showing amount of subsequent treatment.	Adequate treatment during first 2 years.					Inadequate treatment during first 2 years.				
	Final outcome.									
	Total.	Serologically and clinically negative.		Unsatisfactory.		Total.	Serologically and clinically negative.		Unsatisfactory.	
		No.	Per cent.	No.	Per cent.		No.	Per cent.	No.	Per cent.
Unsatisfactory, receiving:										
Heavy metal only	10	3	30.0	7	70.0	28	5	17.9	23	82.1
10 arsenicals or less	42	5	11.9	37	88.1	143	34	23.8	109	76.2
Over 10 arsenicals	33	19	57.6	14	42.4	102	51	50.0	51	50.0
Total	85	27	31.8	58	68.2	273	90	33.0	183	67.0
Serologic relapse or resistant serum, receiving:										
Heavy metal only	9	2	22.2	7	77.8	22	4	18.2	18	81.8
10 arsenicals or less	36	5	13.9	31	86.1	137	33	24.1	104	75.9
Over 10 arsenicals	25	16	64.0	9	36.0	82	40	48.8	42	51.2
Total	70	23	32.9	47	67.1	241	77	32.0	164	68.0
Clinical relapse, receiving:										
Heavy metal only	2	2	100.0
10 arsenicals or less	8	2	25.0	6	75.0	29	9	31.0	20	69.0
Over 10 arsenicals	9	8	88.9	1	11.1	37	21	56.8	16	43.2
Total	19	10	52.6	9	47.4	66	30	45.5	36	54.5
Neurosyphilis and spinal fluid fast, receiving:										
Heavy metal only	2	1	50.0	1	50.0	7	1*	14.3	6	85.7
10 arsenicals or less	10	10	100.0	20	6	30.0	14	70.0
Over 10 arsenicals	16	8	50.0	8	50.0	25	10	40.0	15	60.0
Total	28	9	32.1	19	67.9	52	17	32.7	35	67.3

* This case also had intraspinal treatment.

Granted this point in the management of the resistant early case, is there any justification for the arbitrary continuation of treatment beyond the 2-year period on a species of "general principles," in the patient who has achieved a satisfactory result within the 2-year period? To this, Table 8 contributes some significant information. It appears that in patients clinically and serologically negative at the end of the first 2 years, whether their previous treatment has been adequate (more than 20 arsphenamin injections with the accompanying heavy metal) or inadequate, the proportion

who ultimately relapse or progress into some form of unsatisfactory outcome, regardless of further treatment or not, is only 4.1% for the adequately treated, and 3.7% for the inadequately (533 and 827 cases, respectively). This is tantamount to saying that an uneventful course toward serologic and clinical negativity within 2 years is a species of promise for the future, and has a margin of error, so to speak, of only 4%. Within this margin of error, the highly practical desideratum of a point at which to stop and to substitute observation for further treatment may be defined. *An uneventful course toward recovery justifies the parole of the patient to observation after 2 years of adequate treatment.* To add further stress to the emphasis which adequate as contrasted with inadequate treatment deserves, it may be pointed out that (Table 8) 76% were in the satisfactory classification at the termination of all treatment if they had been adequately treated, while only 57% were in that classification if their first 2 years of treatment had been inadequate.

TABLE 8.—FINAL OUTCOME IN RESISTANT CASES OF EARLY SYPHILIS, SHOWING THE EFFECTIVENESS OF SUBSEQUENT TREATMENT AFTER THE FIRST 2 YEARS OF TREATMENT.

Result at end of first 2 years.	Adequate treatment during first 2 years.				Inadequate treatment during first 2 years.			
	Final Outcome							
	Serologically and clinically negative.		Unsatisfactory.		Serologically and clinically negative.		Unsatisfactory.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Serologically and clinically negative:								
No further treatment . .	206	38.6	4	0.8	153	18.5	2	0.2
Heavy metal only . . .	105	19.7	4	0.8	146	17.7	7	0.8
1 to 10 arsenicals . . .	72	13.5	5	0.9	137	16.6	15	1.8
More than 10 arsenicals .	20	3.8	9	1.7	35	4.2	7	0.8
Total	403	75.6	22	4.1	471	57.0	31	3.7
Unsatisfactory:								
No further treatment . .	3	0.6	22	4.1	5	0.6	43	5.2
Heavy metal only . . .	3	0.6	7	1.3	5	0.6	23	2.8
1 to 10 arsenicals . . .	5	0.9	37	6.9	34	4.1	109	13.2
More than 10 arsenicals .	19	3.6	14	2.6	51	6.2	51	6.2
Total	27	5.1	80	15.0	90	10.9	226	27.3
Total cases*	533				827			

* There were 10 cases where the result of treatment at the end of 2 years was unknown.

The irreducible residue of failure from apparently satisfactory results in the earlier observation periods is 3.7% to 4.1%. From the earlier unsatisfactory result groups the irreducible minimum of

ultimate poor results is 15% with early adequate treatment and 27% with inadequate treatment during the first 2 years. From this statement the fact stands out clearly that syphilis partitions its victims from the outset into "sheep" and "goats," and that taking good treatment and bad, in the aggregate the "goats" will range from 4% to 27%. These percentages may then be thought of as representing the morbidity of syphilis under present-day treatment conditions.

Conclusions. 1. Disregarding treatment systems, the highest proportion of "satisfactory results" in seronegative primary syphilis was obtained with 10 to 19 (preferably the higher number) injections of arsphenamin (with accompanying heavy metal); in seropositive primary syphilis, 25 to 35 injections; in early secondary syphilis (first year), 20 to 29 injections. The good result obtainable with the prolongation of treatment in seropositive primary syphilis is apparent.

2. The proportion of satisfactory results thus obtained for the respective phases is 85%, 65% and 58%, respectively, regardless of system.

3. Poorer results in prolonged treatment are due to the intrinsic resistance of the case, not to the prolongation of treatment.

4. The use of a higher arsphenamin ("606") dosage scale exerts no unfavorable effect on outcome. In fact, there is evidence that a low-dosage scale has definite shortcomings.

5. Neurosyphilitic relapse is higher on a low-dosage than a high-dosage scale when intermittent (rest interval) treatment is used.

6. Arsphenamin adequately used does not predispose to neurosyphilis.

7. Satisfactory treatment results decline from 62% to 9% with progressively increasing grades of neurosyphilitic involvement as indicated by the spinal fluid findings (1090 cases).

8. More than 20 arsphenamin injections with accompanying heavy metal in the first 2 years of syphilis is better than less than 20 injections with heavy metal regardless of system.

9. Failure to get a satisfactory result by 20 injections or less calls for further administration of the arsphenamin. The giving of more than 10 additional injections plus heavy metal may double the proportion of unsatisfactory outcomes reclaimed.

10. In the decision as to when to stop treatment in the ordinary case, an uneventful clinical and serologic course toward recovery is paramount. In such an uneventful course, the parole of the patient to observation after 2 years of adequate treatment is justified.

11. The irreducible margin of failure in the treatment of early syphilis—the proportion of patients not likely to achieve or maintain a satisfactory result by any treatment—ranges from 4% to 27%, depending on method, stage at which treatment begins, adequacy of treatment during the first 2 years of the infection and other considerations discussed in previous papers.

WHAT TREATMENT IN EARLY SYPHILIS ACCOMPLISHES.†

III. COMPARISON OF BRUUSGAARD'S WORK AND THE 3- TO 20-YEAR RESULTS OF THE COÖPERATIVE CLINICAL GROUP.

BY JOHN H. STOKES, M.D., with LIDA J. USILTON, M.A.,* and HAROLD N. COLE, M.D., JOSEPH EARLE MOORE, M.D., PAUL A. O'LEARY, M.D., UDO J. WILE, M.D., THOMAS PARRAN, JR., M.D.,* JOHN McMULLEN, M.D.*

THE material in early syphilis, treated and observed for 3 or more years by the American Coöperative Clinical Group provides an exceptional background against which to project the outcome of untreated early syphilis as presented in Bruusgaard's remarkable evaluation of Cesare Boeck's series of patients untreated by specific methods between the years 1891 and 1910. The syphilis clinic at the Oslo Hospital with which Bruusgaard is connected serves a stable, well-educated population; it has for years been staffed by competent physicians, and between the years 1891-1916 its chief, Dr. Boeck, believed that patients with early syphilis did about as well without any treatment as with the mercurial therapy then in vogue. In these years, 2181 patients diagnosed as primary or secondary syphilis were admitted to the Oslo Clinic. Most of them received no treatment. Some received a little mercury by mouth or potassium iodid or both, but for all practical purposes it can be said that these patients were untreated, or practically so. In the years 1925-1927, Bruusgaard was successful in following 473 of the original 2181 patients; 309 were living and each of these was completely reëxamined physically with special emphasis on the cardiovascular and nervous systems, though routine examination of the cerebrospinal fluid was not carried out. Most of the 164 dead had died in the Oslo Hospital, the cause of death being known; in 40, necropsies had been obtained. The majority of the patients were reëxamined or had died more than 20 years after infection. Only 37% of the total number had developed any active lesion of late syphilis; 22% had died of some unrelated cause, and nearly half of this group had lived for 20 or more years after infection without developing any lesion. In 14% the only evidence of infection was a persistently positive blood Wassermann; in 27 per cent, clinical "arrest" or "cure" seemed to have occurred in spite of the absence of treatment.

With a view to making the appropriate comparisons, the material of the American study was recast into the categories employed

* Names with asterisk represent the U. S. Public Health Service; names without asterisk represent the Coöperative Clinical Group.

† Reference to previous publications by this group is given in a footnote to Part I.

by Bruusgaard. Barring any items of statistical disparity in that our group of 3- to 10-year cases is 821 in number in contrast with Bruusgaard's 79, and that we are unable to make precise comparisons of cardiovascular examination technique in the two groups, the two series of living patients stand parallel analysis very well. The notable thoroughness and extended range of Bruusgaard's physical examinations compensate to some degree for the comparative lack of spinal fluid studies, and his radiography of the heart and great vessels makes conclusions in the cardiovascular field fairly safe. Our 10-to 12-year group numbers 86, as compared with his 66 patients; our total number of cases considered, 907 (13.3% of our 6807 early syphilis patients) as compared with his 145 patients living at the time of the examination (6.6% of his total of 2181 patients with early syphilis).

It should be explained that Bruusgaard's inclusion of tabetic and parietic residua as syphilis was reduplicated in our own series, but that, as with Bruusgaard, all other scars or residua of the disease were excluded from the category of active syphilis. In the category of cardiovascular syphilis it is possible that the lack of definition of signs and symptoms accepted as evidence of involvement modifies the results in the living patients, for Bruusgaard's series includes a number of patients who had long shown signs of this type of involvement, while the shift in our clinical material has tended in the later years toward earlier recognition of symptoms and signs on the basis of routine periodic clinical examination.

The comparison of deaths has been excluded from the study because the procedure for the collection of the data on deaths varied in the two series. Bruusgaard followed his patients through the vital statistics office of Denmark, securing the cause of death in every possible case. The Coöperative Clinical Group did not make a similar effort through the vital statistics office of each of the states of the United States. The only cases of death which are recorded in the Coöperative Clinical material are those found through the social service follow-up of patients who lapsed from treatment before the maximum benefit had been received, or those who died within the institution of which the clinic treating the patient in the early stage of syphilis was an integral part. Deaths among those patients who had received an adequate amount of antisypilitic treatment and been serologically and clinically negative for one year or more are unknown, unless before death it had happened that the patient had returned to the clinic treating his early syphilis with some late manifestation of the disease. That Bruusgaard's efforts were more effective in collecting data on deaths than those of the Coöperative Clinical Group is apparent from the proportion of deaths from all causes among his cases. In the 3- to 10-year material, Bruusgaard found 14 deaths per 100 cases as against 1 among the early cases treated by the Coöperative Clinical Group. In the

10- to 20-year material there were only 2 deaths from any cause recorded in the Coöperative Clinical material of 88 cases of syphilis as compared with 58 in 124 cases in the Bruusgaard material. However, since 14 of the 58 deaths in 124 patients in Bruusgaard's 10- to 20-year material had a cardiovascular or central nervous system involvement, whereas there was only 1 death from cardiovascular syphilis and none from central nervous system syphilis in the 88 cases of syphilis followed by the Coöperative Clinics for a similar period of time, one might safely assume that early and adequate treatment certainly has had at least a tendency to prolong life and to some extent control the late manifestations of syphilis. On the other hand, the good results obtained among the living patients in our series are at a minimum. The living patients in the Coöperative Clinical Group material, who remained under treatment or observation for 3 to 10 or 10 to 20 years, consist largely of those whose syphilis was of a relapsing or resistant type or those who had received inadequate and irregular treatment during the early stage of syphilis. Those patients who had responded well to treatment had to a large extent disappeared. For example, a third of the patients who had been under observation or treatment for 2 years were lost sight of by the beginning of the third year. Bruusgaard's follow-up and reëxamination of every available patient gives the end results of untreated syphilis the benefit of all readily responsive infections. Therefore, any evidence of good results in the Coöperative Clinic cases represents the very minimum of the effectiveness of treatment in controlling syphilis. With these considerations in mind we take up Table 9.

TABLE 9.—THE OUTCOME IN TREATED AND UNTREATED EARLY SYPHILIS (BASED ON LIVING PATIENTS ONLY).

Status of patient at time of final examination.	Treated cases in 5 co-operating clinics in the U. S.				Bruusgaard's analysis of Boeck's untreated cases.			
	Interval between infection and final examination.				Interval between infection and final examination.			
	3 to 10 years.		10 to 20 years.		3 to 10 years.		10 to 20 years.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Neurosyphilis	11	1.4	8	9.3	4	5.1	11	16.7
Cardiovascular:								
Definite	6	0.7	5	5.8	1	1.5
Suspicious	10	1.3	4	4.6				
Skin, mucosal or bone syphilis	16	2.0	1	1.2	27	34.2	21	31.8
Symptom-free with:								
Positive Wassermann	144	17.6	14	16.3	29	36.7	9	13.6
Negative Wassermann	634	77.0	54	62.8	19	24.0	24	36.4
Total	821	100.0	86	100.0	79	100.0	66	100.0

In Table 9, Bruusgaard's 3- to 10- and 10- to 20-year observation groups of living patients are paralleled with ours. Clinical neuro-

syphilis appears in 1.4% of our 3- to 10-year group; in his untreated cases in 5.1% within the same period. In our 10- to 20-year group it appears in 9.3% as compared with 16.7% of his untreated cases. There can be no question in this field of the worth of treatment.

Late skin, mucosal and bone syphilis appears in our treated 3- to 10-year group in 2% of cases; in Bruusgaard's in 34.2%. In the 10- to 20-year group our material shows 1.2%; Bruusgaard's 31.7%. This is an interesting commentary on the way in which modern treatment has done away with benign symptomatic syphilis. It is also discussable in the light of Brown and Pearce's theory of the rôle of reaction in bone and skin as a form of systemic defense in syphilis.

In the symptom-free but Wassermann-positive category our series includes 17.6% after 3 to 10 years; Bruusgaard's series 36.7%. In the 10- to 20-year group, we have 16.3%; he has 13.6%. Our figures suggest that we are dealing in the 10th to the 20th year with our irreducible minimum of fixed positive asymptomatic cases, which is almost identical with his group without treatment.

In the symptom-free Wassermann-negative group we have 77%, while Bruusgaard has only 24% in the 3- to 10-year period, and 62.8% as compared with 36.4% in the 10- to 20-year period. Inasmuch as these constitute, so far as present-day criteria go, the "cured" patients, the vindication of modern treatment methods within the limitations of this investigation is complete.

TABLE 10.—SPINAL FLUID EXAMINATIONS ON PATIENTS WITH EARLY SYPHILIS CLASSIFIED AS SYMPTOM-FREE, BLOOD WASSERMANN POSITIVE OR NEGATIVE AT TERMINATION OF TREATMENT (BASED ON LIVING PATIENTS ONLY).

Spinal fluid examination on termination of treatment.	Interval between infection and final examination.			
	3 to 10 years.		10 to 20 years.	
	No.	Per cent.	No.	Per cent.
<i>Symptom-free, positive Wassermann.</i>				
Spinal fluid:				
Not made	39	4.8	2	2.3
Negative	68	8.3	9	10.5
Positive during treatment, negative at end	8	1.0		
Positive at end of treatment	19	2.3	2	2.3
Positive during treatment, unknown at end	10	1.2	1	1.2
Total cases symptom-free, positive Wassermann:				
Coöperating Clinics	144	17.6	14	16.3
Boeck's cases	29	36.7	9	13.6
<i>Symptom-free, negative Wassermann.</i>				
Spinal fluid:				
Not made	97	11.8	9	10.5
Negative	454	55.3	41	47.8
Positive during treatment, negative at end	48	5.8	2	2.3
Positive at end of treatment	12	1.5	1	1.2
Positive during treatment, unknown at end	23	2.8	1	1.2
Total cases symptom-free, negative Wassermann:				
Coöperating Clinics	634	77.2	54	62.8
Boeck's cases	19	24.0	24	36.4

It is now essential to point out, though another tabular study is necessary to do so (Table 10), that had spinal fluid examinations been performed in an equally large proportion of Bruusgaard's patients as compared with our own, the blood serologic groups just discussed would have sustained a slightly different interpretation. Of the seropositive patients in our series, 2.3% have been aligned with the neurosyphilitic group in both the 3- to 10- and 10- to 20-year periods by examination of the spinal fluid. It is impossible to guess how many of Bruusgaard's untreated patients would have fallen in the same category (asymptomatic neurosyphilis). Among the seronegative patients in our series, even 1.5% and 1.2% of abnormal spinal fluids appeared at final examination after 3 to 10 and 10 to 20 years, respectively.

Bruusgaard found no cardiovascular syphilis in untreated patients (living) in the 3- to 10-year group, and only 1.5% in the 10- to 20-year period. In the 20- to 30-year Bruusgaard group, 10% appears, and in the 30- to 40-year group, 12.5%. We have, of course, no comparable groupings for the later years, but for the 3- to 10-year period 0.7% of cardiovascular syphilis is definitely recognized, and 1.3% of suspicious cases (dilated aorta by Roentgen ray). In the 10- to 20-year period we recognize 5.8% definitely and 4.6% as open to suspicion, where Bruusgaard finds only 1.5%.

Whether these rather marked differences are entirely ascribable to differences in examination technique, or whether we are witnessing here a genuinely predisposing or at least hastening effect of treatment, it is impossible from this material to say. As has been previously suggested, there is reason to think from Bruusgaard's description of his material that his cardiovascular cases were usually recognized at a later stage than ours.

With the reservations already set forth with regard to deaths in mind, as well as the fact that we have too small a statistical sample in either material from which to draw any definite conclusions, it is still worth while to observe that in the 3- to 10-year period Bruusgaard averages 1 death, with a definite cardiovascular involvement per 100 cases of syphilis, as compared with our 1 death, with a cardiovascular involvement in 500 cases of syphilis. In the 10- to 20-year period there were no deaths with a cardiovascular involvement in the 88 cases of syphilis treated and observed in our clinics, as compared with 10 deaths per 100 cases in Bruusgaard's series.

We have undertaken to examine Bruusgaard's classifications of his cases as applied to our own material, in terms of the various types of treatment which our patients received, in order to see whether principles such as we have recognized in previous studies apply with equal force to his typing of material in long periods of observation (over 3 years).

It appears that under "inadequate treatment" (less than 20 injections of arsphenamin and the accompanying heavy metal),

93% of our patients in the 3- to 10-year group achieved freedom from symptoms with a positive or negative Wassermann, while 60.7% of Bruusgaard's patients, untreated, achieved the same status. In the 10- to 20-year period, 85% of our patients achieved this same status, as against 50% of Bruusgaard's. Thus, even inadequate treatment holds a substantial lead over no treatment in the comparisons of these two series.

Adequate treatment in the 3- to 10-year period gave 96% symptom-free with Wassermann positive or negative for our series, while Bruusgaard's series shows 60.7%. In the 10- to 20-year period, treated cases stand at 74%, untreated at 50%. In Table 11 is given the classification on the basis of adequate and inadequate treatment by the continuous, intermittent and irregular schemes.

TABLE 11.—THE OUTCOME OF ADEQUATELY AND INADEQUATELY TREATED EARLY SYPHILIS BY THE CONTINUOUS, INTERMITTENT AND IRREGULAR SCHEMES OF TREATMENT FOR PATIENTS UNDER TREATMENT OR OBSERVATION FROM 3 TO 20 YEARS IN THE 5 COÖPERATING CLINICS IN THE UNITED STATES (BASED ON LIVING PATIENTS ONLY).

Status of patient at time of final examination.	1 to 19 doses of arsphenamin with heavy metal.						20 or more doses of arsphenamin with heavy metal.					
	Continu-ous.		Intermit-tent.		Irregular.		Continu-ous.		Intermit-tent.		Irregular.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
<i>3 to 10 years.</i>												
Neurosyphilis	1	2.4	1	0.7	6	2.9	1	0.5	2	1.2
Cardiovascular:												
Definite	3	1.4	3	1.8
Suspicious	1	2.4	1	0.7	2	1.0	2	3.2	4	2.0		
Skin, mucosal or bone syphilis	1	0.7	11	5.3	1	1.6	1	0.5	2	1.2
Symptom-free:												
Positive Wassermann	8	19.0	13	9.3	64	30.8	3	4.7	23	11.2	33	20.3
Negative Wassermann	32	76.2	124	88.6	122	58.6	57	90.5	176	85.8	123	75.5
Total	42	100.0	140	100.0	208	100.0	63	100.0	205	100.0	163	100.0
<i>10 to 20 years.</i>												
Neurosyphilis	2	7.4	6	14.3
Cardiovascular:												
Definite	2	7.4	3	7.1
Suspicious	1	3.7	3	7.1
Skin, mucosal or bone syphilis	1	3.7						
Symptom-free:												
Positive Wassermann	1	33.3	6	22.2	1	20.0	6	14.3
Negative Wassermann	2	66.7	9	100.0	15	55.6	4	80.0	24	57.2
Total	3	100.0	9	100.0	27	100.0	5	100.0	42	100.0

The analysis of this material (Table 11) on the basis of system of treatment, in both the inadequate and adequate groups, shows very clearly that it is irregular treatment which is largely responsible for the unsatisfactory outcomes. For example, in the 3- to 10-year period among inadequately treated patients, neurosyphilis, cardiovascular syphilis, and especially late skin, mucosal and bone

syphilis, occur mainly in the group of irregularly treated patients. In the 10- to 20-year period, they occur exclusively in patients whose treatment has been irregular.

The significance of the symptom-free Wassermann-positive group of patients, which one would ordinarily hesitate to admit to the category of benign or innocent syphilis, could not be discussed from Bruusgaard's cases owing to the lack of spinal fluid examinations in his series. It interested us, however, to see how relatively small a proportion of such cases after 3 to 20 years had abnormal fluids under either inadequate or adequate treatment. In the former case only 1.5% had abnormal fluids, while after adequate treatment 3% were abnormal. The presumption that the adequately treated cases were on the whole the more resistant applies here. It is, however, borne out here, as in the previous discussion, that by far the largest part of the spinal fluid abnormalities fall in the group of irregularly treated cases.

The examination of the symptom-free seronegative group which passes usually as clinical and serologic cure in most reports, shows that even freedom from symptoms and a negative blood do not invariably mean a normal spinal fluid. In the 3- to 10-year group, adequately but irregularly treated, there will be as high as 4.5% of patients who have abnormal spinal fluids in spite of their negative bloods and freedom from symptoms.

Summary. 1. A comparison is made of 907 cases of treated early syphilis (Coöperative Clinical Group) with 145 cases of untreated early syphilis (Bruusgaard series) observed from 3 to 10 and 10 to 20 years.

2. Clinical neurosyphilis is from 2 to 4 times as frequent in the untreated as in the treated cases.

3. The frequency of bone and skin lesions in untreated cases is 17 to 26 times as great as in treated cases.

4. Treatment renders 77% to 63% of patients symptom-free and Wassermann-negative in the 3- to 20-year observation period, as compared with 24% to 36% without treatment.

5. Even seronegative treated patients will present 1.5% to 1.2% abnormal spinal fluids after 3 to 20 years.

6. Adequate treatment by an effective technique gives 96% symptom-free patients with positive or negative blood tests after 3 to 10 years, while *no* treatment gives 61%.

7. In the 10- to 20-year observation period, the same treatment gives 74%; *no* treatment, 50%.

8. Complications develop largely in irregularly treated patients. The proportion of abnormal spinal fluids in such patients, otherwise negative, may reach 4.5% in the 3- to 10-year period.

9. The cardiovascular results are interpreted.

10. While the relative benignity of many aspects of untreated syphilis is conceded, the results summarized in Items 4 and 6 fully justify adequate and systematic modern treatment for early syphilis.

THE RELATIONSHIP BETWEEN ANTISYPHILITIC TREATMENT AND TOXIC CIRRHOSIS.*

BY C. W. BALDRIDGE, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, UNIVERSITY OF IOWA COLLEGE OF
MEDICINE, IOWA CITY, IOWA.

(From the University of Iowa College of Medicine.)

Is it possible that antisyphilitic treatment consisting of mercury and arsphenamin may produce toxic cirrhosis? If toxic cirrhosis follows antisyphilitic treatment is this possible in a liver not previously damaged by syphilis?

Excluded from consideration here are the established ill effects of antisyphilitic treatment upon the liver such as that described by Wile¹ as a "therapeutic paradox" and severe acute yellow atrophy even though it be called "acute cirrhosis."²

In 1929 O'Leary, Green and Rowntree³ reported 1 case which they called "treatment cirrhosis." This case was that of a man with a mildly positive Wassermann reaction on one occasion who, according to the authors was probably non-syphilitic, but who received 7.9 gm. of arsphenamin, 36 injections of mercury and 200 innuncations of mercury over a period of 5 years. The patient took an unknown amount of treatment from other physicians during the succeeding 5 years. Ten years after the beginning of treatment the patient returned to The Mayo Clinic with ascites and a few months later died of a ruptured esophageal varix. There was no history of alcoholism. The liver was cirrhotic and was reduced in size. In later publications O'Leary^{4,5} mentioned the danger of producing cirrhosis of the liver by the administration of arsphenamin, but did not make clear whether or not he felt that this was possible in the absence of hepatic syphilis. Hutchinson,⁶ Hamburger,⁷ Stockman,⁸ and O'Leary, Snell and Bannick⁹ have reported cases in which cirrhosis or at least portal obstruction has been attributed to the long continued use of inorganic arsenic. Moreover, the "epidemic" of cirrhosis which occurred in England during 1900 and 1901 was attributed to arsenic in beer.^{10,11} Sollmann¹² in his textbook makes the statement that liver degeneration is more marked after inorganic than after organic arsenic compounds.

O'Leary and his coauthors have been vague in dealing with the etiologic relationship of antisyphilitic treatment to cirrhosis but this vagueness has been invoked advisedly. When cirrhosis follows treatment in a syphilitic subject, it is obviously difficult or impossible to be sure that the liver had not been damaged to some extent by syphilis before treatment was begun. Probably all syphil-

* Presented before the Sixth Annual Meeting of the Central Society for Clinical Research, Chicago, October 27, 1933.

ologists admit that vigorous treatment with arsphenamin may cause an increase in the portal obstruction in cases of hepar lobatum. Sudden increase in scar formation without actual damage to liver cells might account for this. That the long continued use of Fowler's solution occasionally results in cirrhosis or that arsenic mixed with beer contributed to the production of cirrhosis in the cases reported from England is generally admitted. That arsphenamin preparations can produce acute necrosis of liver cells seems to be established although many ingenious explanations for postarsphenamin jaundice have been advanced.¹³

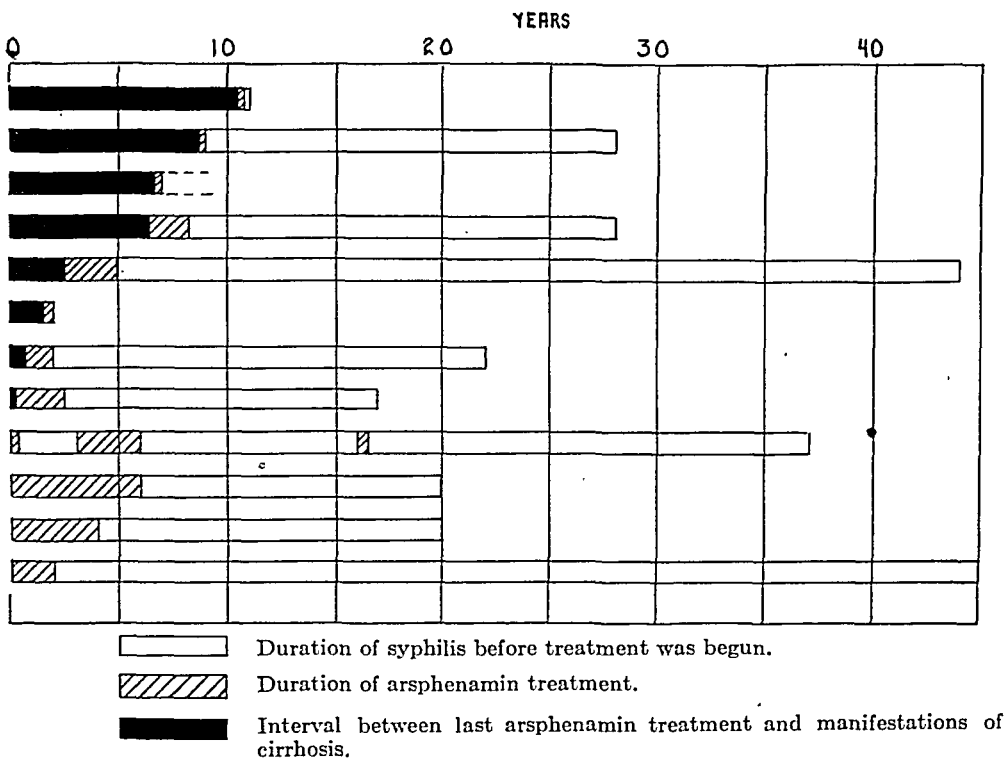


CHART I.

In going over the records of patients admitted to the University Hospital since 1921, with conditions resembling cirrhosis, many cases were unsatisfactory for a study such as this. Twenty-one cases of Banti's syndrome, 2 of Felty's syndrome, 8 of Pick's syndrome, 5 of hemochromatosis, and 3 of cinchophen poisoning were excluded. Furthermore, all patients with enlarged livers were excluded, not because it was completely justifiable, but because in this particular study interstitial syphilis of the liver could not be completely ruled out in such cases except by necropsy.

In 20 of our cases of syphilis of the liver the process was not extensive enough to produce portal obstruction. All of these patients

received mercury by innunction and potassium iodid and 9 were treated with arsphenamin. Of the 9 who received arsphenamin 2 developed jaundice after treatment, and in 1 there was also transitory ascites. Most of these 20 patients improved a great deal under treatment.

In 14 other cases the hepatic syphilis was extensive, the spleen was enlarged, and there was portal obstruction. Three of these patients had received arsphenamin before they came to the hospital and 1 was given arsphenamin cautiously while in the hospital. In all 4 the portal obstruction increased after arsphenamin treatment (a therapeutic paradox). Most of the other 10 patients improved under treatment with potassium iodid and mercury or bismuth. One case was much benefited by a splenectomy, after which arsphenamin treatment did not cause ascites. The above 34 cases of hepatic syphilis were excluded from consideration in this study. After eliminating all of the above, as well as all non-fatal cases of probable portal cirrhosis which did not require repeated paracentesis, and all cases complicated by cardiac decompensation, there were only 36 cases remaining in the series.

Of these 36 cases 15 had syphilis. This incidence of syphilis among patients with portal cirrhosis is higher than that found by Symmers¹⁴ in New York and lower than that observed by DeDuc¹⁵ at Ann Arbor. At least 11 of the 15 patients with syphilis received antisyphilitic treatment before cirrhosis became manifest and 1 non-syphilitic patient also received antisyphilitic treatment. The duration of the syphilitic infection, the amount and the nature of treatment, and the relation of these to the onset of cirrhosis is indicated in the chart and table.

It is to be noted that in one-third of our patients in whom a definite diagnosis of portal cirrhosis could be made, there was a history of antisyphilitic treatment preceding the clinical evidence of cirrhosis. Vices are prone to be multiple, so that alcoholism, syphilis and antisyphilitic treatment often coexist in the history of patients with cirrhosis of the liver. In the presence of multiple factors which may bear on the etiology of disease, the clinician usually looks to the pathologist for a decision, but in this instance an authoritative opinion can be rendered only by the most experienced pathologist. The cases in this series present several circumstances which tend to incriminate antisyphilitic treatment in the causation of cirrhosis of the liver.

Three of the patients in whom cirrhosis followed antisyphilitic treatment were women whose denial of alcoholism carried conviction. One man would not admit the use of alcohol while one other stated that he had taken alcohol in small amounts but had been an almost total abstainer for a period of 14 years before cirrhosis was recognized. Snell¹⁶ states that cirrhosis usually does not progress except during the period of exposure to the injurious agent. If we

admit the validity of Snell's statement, then the patient who had abstained from alcohol for 14 years might be classed with the 4 who never used alcohol. Four other patients used alcohol occasionally and moderately, but 3 drank to excess for many years. While the incidence of portal cirrhosis is not very high, even in confirmed alcoholics, the possibility of this type of liver damage must be admitted in at least 3 of these 12 cases.

In 7 of the cases the Wassermann reaction was completely negative when cirrhosis developed, and in 3 others the alcoholic antigen gave negative reactions. In only 2 did the Wassermann reaction remain strongly positive. The fact that most of the patients had vigorous treatment and developed cirrhosis at a time when the Wassermann reaction was negative, speaks against the probability of the liver damage being dependent upon the syphilitic infection. The variable duration of the syphilis before cirrhosis appeared and the fact that 1 patient never had syphilis, are other points against the theory that the cirrhosis in these patients may have been due to syphilis.

TABLE 1.

Case.	Age.	Sex.	Alcohol.	Arsphenamin injections.	Mercury.	Wassermann reactions.†			
						Before treatment.		After treatment.	
						Alc.	Chol.	Alc.	Chol.
1 . . .	41	M	++++	6	Moderate amount	4+	4+	0	4+
2 . . .	54	M	+*	5	Little	?	?	0	0
3 . . .	56	M	++	10	Moderate amount	4+	4+	4+	4+
4 . . .	46	F	0	27	Much	4+	4+	0	0
5 . . .	65	M	++++	36	Much	4+	4+	0	3+
6 . . .	54	F	0	?	Too much	0	0	0	0
7 . . .	40	M	0	42	Much	4+	4+	3+	4+
8 . . .	44	F	0	12	Much	4+	4+	0	0
9 . . .	62	M	++	37	Much	4+	...	0	0
10 . . .	35	M	++	23	Much	4+	4+	0	0
11 . . .	39	M	++	18	Much	4+	4+	0	4+
12 . . .	76	M	+++	?	?	4+	4+	0	0

* Used practically no alcohol for 14 years before cirrhosis appeared.

† The Wassermann technique included fixation in the icebox for 4 hours and antigens as indicated.

Undoubted signs of cirrhosis appeared in 6 of the cases within 8 months or less after combined treatment with mercury and arsphenamin. In Case 9 ascites developed after intensive anti-syphilitic treatment and a subsequent injection of arsphenamin was followed by an increase in the amount of ascites. Treatment was then stopped after which the signs of portal obstruction disappeared and the patient has remained free from ascites for 3 years. The ascites also increased in Case 11 under arsphenamin treatment.

In two instances there were signs of arsenic poisoning evidenced by peripheral neuritis in 1 and arsenical dermatitis in the other. One patient suffered from rather marked mercurial poisoning.

Case 6 is of particular interest in that there was never any evidence of syphilis, even in the necropsy findings. This patient took anti-syphilitic treatment at her own insistence and developed mercury poisoning in 1923. We were unable to determine the extent of the arsphenamin treatment. In 1925 a "hob-nail liver" was discovered at operation and in 1927 she developed ascites and died. In this case syphilis and alcohol can be definitely excluded.

All of the 12 patients considered here received both arsphenamin and mercury. Strathy, Smith and Hannah¹⁷ have suggested that the kidney damage occasioned by mercury might be a predisposing factor in the toxic effects of arsphenamin. In no case was there a history of postarsphenamin jaundice and no symptom which would suggest a non-fatal acute yellow atrophy of the liver was observed while the patients were under treatment. Seven of the patients received part or all of their treatment at the University Hospital.

Necropsies were obtained in 16 of our 36 cases of atrophic cirrhosis. Among the 16 cases in which necropsy studies were made there were 4 syphilitic subjects. Three of these had received antisyphilitic treatment. A necropsy was also obtained in the 1 patient (Case 6) who was non-syphilitic but who had received antisyphilitic treatment. Sections of the livers from all 16 cases were submitted to Dr. F. B. Mallory for an opinion.

The sections submitted included one from the liver of a man who had had untreated syphilis for 40 years, but who was also a confirmed alcoholic. Dr. Mallory commented on the section as follows: "Old alcoholic. Slight hyalin present."

In Case 11 there was a history of moderate alcoholism (wine) and the outstanding feature in addition to cirrhosis was polycythemia with cyanotic and painful extremities. The patient was syphilitic and received 18 injections of neoarsphenamin. A small amount of ascites existed at the beginning of the last course of 6 injections, but the fluid in the abdomen increased rapidly during and after these treatments. Dr. Mallory considered that the cirrhosis in this case was probably on an alcoholic basis but he could find no hyalin.

In Cases 6, 8 and 10 Dr. Mallory believed the cirrhosis to be the result of a previous acute yellow atrophy (toxic cirrhosis¹⁸).

There is every reason to expect toxic cirrhosis as one of the complications of antisyphilitic treatment. Any toxic principle which is capable of producing acute yellow atrophy may also produce toxic cirrhosis. The fact that cirrhosis followed antisyphilitic treatment in 2 non-syphilitic subjects is strong evidence that such treatment can produce this liver lesion alone without the predisposing influence of hepatic syphilis. In our non-syphilitic patient (Case 6) the cirrhosis was of the toxic type and the gross description of the liver

in the case of "treatment cirrhosis" reported by O'Leary, Green and Rowntree is also compatible with a diagnosis of toxic cirrhosis. The histologic changes in the livers of the syphilitic cases, 8 and 10, were the same as those in the non-syphilitic subject (Case 6).

The author does not wish to imply that toxic cirrhosis is a hazard of major importance in the treatment of syphilis with arsphenamin. However, the evidence would seem to substantiate the claim that toxic cirrhosis of the liver may result from antisyphilitic treatment *per se*. In Iowa, cirrhosis of the liver is not common but a surprising number of the patients seen here with cirrhosis of the liver have had antisyphilitic treatment (at least 12 out of 36).

All of the 12 patients in this series, in whom cirrhosis followed antisyphilitic treatment, received arsphenamin or neoarsphenamin or both between 1917 and 1926. This is in keeping with Dr. Mallory's observation that liver damage following arsphenamin was more common for a few years after the introduction of American-made drugs than it was either before or since.

Summary. Twelve patients are reported in whom cirrhosis of the liver with portal obstruction followed antisyphilitic treatment with arsphenamin and mercury. Clinical evidence of disease of the liver was not found in any case before antisyphilitic treatment was begun.

In 3 of the 4 patients who came to necropsy the cirrhosis was of the toxic type, *i. e.*, the result of a previous acute yellow atrophy.

The author wishes to express his appreciation for the help given by Drs. F. B. Mallory, F. Parker, Jr., and P. A. O'Leary.

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RECURRENT LARYNGEAL PARALYSIS IN LEFT VENTRICULAR FAILURE.*

By FREDERICK H. KING, M.D.,
EMANUEL LIBMAN FELLOW, MOUNT SINAI HOSPITAL,

WILLIAM M. HITZIG, M.D.,
EUGENE MEYER FELLOW IN PATHOLOGY, MOUNT SINAI HOSPITAL,

AND

ARTHUR M. FISHBERG, M.D.,
ASSOCIATE PHYSICIAN TO BETH ISRAEL HOSPITAL; ASSOCIATE IN MEDICINE, MOUNT SINAI HOSPITAL, NEW YORK CITY.

(From the Medical Service of Dr. George Baehr and the Laboratories of The Mount Sinai Hospital.)

THE occurrence of left recurrent laryngeal palsy in exceptional instances of mitral stenosis is well known. So far as we have been able to find, this palsy has not been described as a manifestation of any other intrinsic disease of the heart, although it may be produced by aneurysm or diffuse dilatation of the aorta and very rarely by pericardial disease.

Recently, we have observed the development of left recurrent laryngeal paralysis in 3 instances of the arteriosclerotic type of heart disease with failure of the left ventricle. In 2 of the cases there was coronary thrombosis, while the third had left ventricular failure, due to chronic glomerulonephritis and coronary arteriosclerosis. The cases seem worthy of description not only because recurrent laryngeal paralysis has not been reported as a complication of coronary thrombosis or other forms of left ventricular failure, but also because they seem to throw light on the pathogenesis of the same palsy in mitral stenosis.

Report of Cases. CASE 1.—A woman, aged 57, was admitted because of precordial pain and dyspnea. For several years she had had occasional aches in the precordial region. Two weeks before admission she was awakened from sleep by agonizing substernal pain. This persisted for almost 12 hours, when it was relieved by a hypodermic injection. The pain was accompanied by orthopnea, profuse perspiration and fever. *The day after the attack she became hoarse and remained so.* The day before admission she had another, almost identical, episode of precordial pain.

On physical examination, the patient was seen to be orthopneic. The lips and nail beds were cyanotic. The temperature was 99° F., the heart rate 100. Presystolic gallop rhythm was audible inside the apex and the second sound was louder at the pulmonic than at the aortic area. Blood pressure was 120/80 mm. The edge of the liver was felt 4 cm. below the costal margin. There was marked edema about the ankles. *Laryngoscopic examination revealed complete paralysis of the left vocal cord, which was in the cadaveric position.*

* Aided by a grant to The Emanuel Libman Fellowship Fund in memory of Adele Schiff.

The teleoroentgenogram (Fig. 1) revealed marked enlargement of the heart to the left. The vascular shadows extending from either hilum were markedly accentuated and broadened. Both lung fields exhibited coarse mottling, diminishing from hilum to periphery, due to intense engorgement and distention of the pulmonary vessels. The electrocardiogram showed left axis deviation. T_2 and T_3 were inverted.

The patient was given an injection of merbaphen, which produced copious diuresis. With this, the edema disappeared and the liver became impalpable. At this time, the venous pressure was found by direct measurement to be 8 cm. of water, a normal value. The evidences of intense pulmonary engorgement persisted. From the point of view of circulatory dynamics, therefore, the patient was suffering, at this time, from left ventricular failure, a disturbance characterized by engorgement of the pulmonary circuit accompanied by normal systemic venous pressure.

The patient's condition became steadily worse. Toward the end there were added to the manifestations of insufficiency of the left heart such evidences of right ventricular failure as rise in venous pressure to 12 cm., dependent edema, bilateral pleural effusions and enlargement of the liver. The electrocardiogram changed to that of the common type of bundle-branch block. The left recurrent laryngeal paralysis persisted. Pulmonary edema developed and the patient succumbed 7 weeks after admission.

Necropsy was performed 5 hours after death. The larynx showed no changes.

The *mediastinum* was carefully dissected. No neoplasm, mediastinitis or lymphadenopathy was found. The left vagus nerve was traced and the recurrent branch followed from its origin to the larynx. About 3 cm. from its origin a segment of the left recurrent laryngeal nerve, about 0.5 cm. in length, was definitely constricted and exhibited bluish discoloration. The constricted and discolored portion of the nerve was that which lay between the arch of the aorta above and the left pulmonary artery below, and abutted against the obliterated ductus arteriosus medially. Proximally and distally to this area, the nerve showed no gross changes.

The *heart* was enlarged. There was moderate hypertrophy and dilatation of both ventricles; the auricles were also dilated, the right more than the left. A circular area, about 1 inch in diameter, on the anterior surface of the left ventricle above the apex was purplish-red in color, dimpled when unsupported and felt soft (microscopically, there was degeneration of the muscle fibers in this area with which was intermingled young connective tissue). The myocardium of the lower two-thirds of the interventricular septum and the anterior and apical portion of the left ventricle showed fibrosis. The mitral and other valves were negative. There was severe arteriosclerosis of both coronaries. In the anterior descending branch of the left coronary artery was a grayish-brown thrombus which completely obliterated the lumen and extended distally about 3 cm. There was an organized thrombus in the right coronary artery about 1 cm. from its origin.

The pulmonary artery and its branches exhibited discrete atheromatous plaques. They were hardly, if at all, dilated, the root of the pulmonary artery measuring 8.5 cm. in circumference. There were adherent thrombi in some of the branches of the pulmonary artery.

Both pleural cavities contained clear fluid. The lungs were markedly engorged and edematous. The cut surface had a rusty tint and there was an infarct in either lower lobe.

The liver extended about 5 cm. below the costal margin, was firm, brownish-red in color and considerably engorged.

Dr. J. H. Globus was kind enough to examine the left vagus and recurrent laryngeal nerves, with the following results:

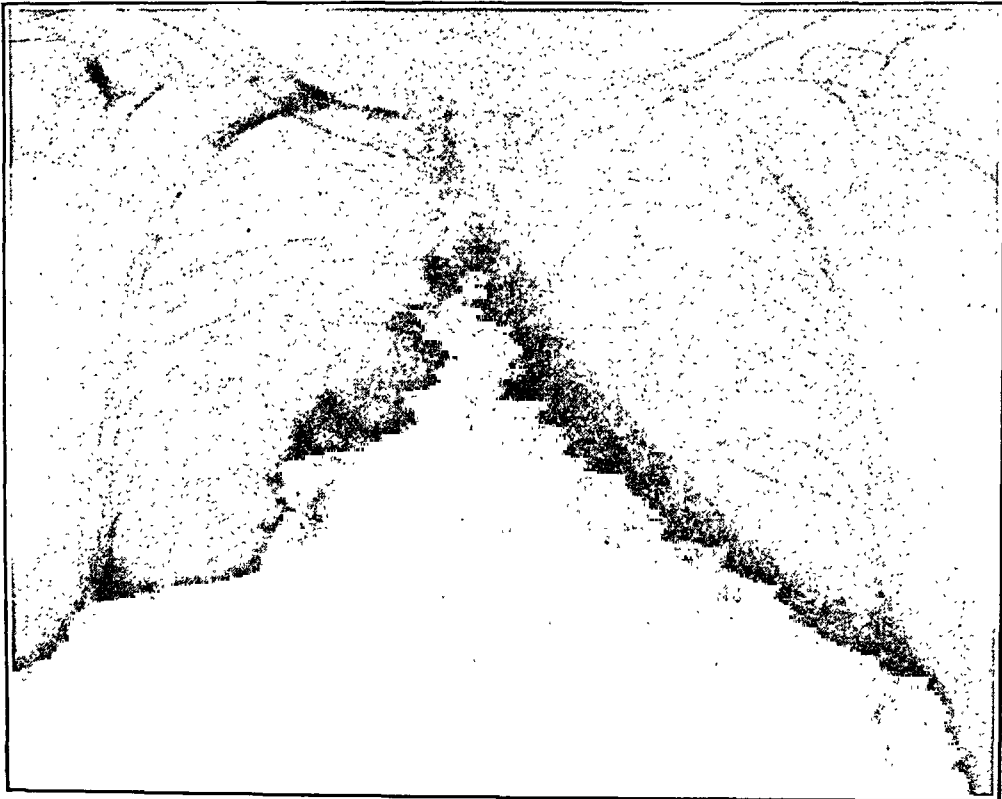


FIG. 1.—Teleoroentgenogram of Case 1. Intense pulmonary engorgement. Note especially the thick and dense shadows cast by the distended primary and secondary branches of the pulmonary artery.



FIG. 2.—Teleoroentgenogram of Case 3. Pulmonary engorgement similar to that in Fig. 1.

Section A—*left vagus nerve proximal to the origin of the left recurrent laryngeal nerve:* Marchi preparation showed quite marked and diffuse myelin degeneration.

Section B—*left recurrent nerve at the point where it passes under the aortic arch and above the left branch of the pulmonary artery:* Marchi preparation showed fairly marked degeneration, approximately as at A.

Sections C and D—*left recurrent laryngeal nerve distal to B:* Marchi preparation showed occasional small deposits of fat with grayish discoloration of some myelin rings.

Section E—*left recurrent laryngeal nerve, 1 cm. distal to D:* Marchi preparation displayed a larger number of fat deposits, some of which showed loss of ring outline and assumed the character of plaques.

Weigert preparations revealed few definite changes, possibly because the degenerative process was not sufficiently massive to be revealed by this method.

Comment on the Histologic Findings. The Marchi preparations indicate fairly marked degeneration of the left recurrent nerve at the point of most probable compression and distally. It is, however, difficult to explain the more marked degeneration in the segment taken from the vagus trunk unless it is assumed that afferent fibers coursing from the recurrent laryngeal nerve upward in the vagus have also been affected by the compression and have undergone degenerative changes.

CASE 2.—A man,* aged 36, was admitted complaining of precordial pain, orthopnea and cough. Three years previously he had been found to have a systolic blood pressure of 200 mm. He felt well until 1 year before admission, when he began to have attacks of precordial pain. These pains recurred frequently and were often incited by exertion. Three weeks before admission, while driving an automobile, he began to cough up large volumes of pink, frothy fluid; at the same time he had viselike precordial pain radiating down the left arm. A week later he had a similar attack following coitus. Ten hours before entering the hospital he had a third attack of pulmonary edema accompanied by precordial pain.

On admission, the patient was coughing up frothy, bloody sputum. The heart was enlarged to the left. The rate was rapid and presystolic gallop rhythm was heard. Moist râles were audible in both lower lobes. The liver edge was 2 cm. below the costal margin. Arterial pressure was 120/102 mm., then falling to 106/80 mm. Venous pressure was 6.5 cm. The electrocardiogram was definitely indicative of recent infarction in the posterior portion of the left ventricle in the part usually supplied by the right coronary artery. There was nodal rhythm with a rate of 115. The R-T interval was elevated in the second and third leads. T was inverted in the second and third leads and there was a large Q wave in the third lead.

Five days after admission, Dr. Rabinowitz noted that the patient was hoarse. The hoarseness persisted to the end. Two laryngoscopic examinations at an interval of a week revealed *left abductor paralysis*. Fifteen days after admission the patient suddenly succumbed. Necropsy was not permitted.

CASE 3.—A conductor, aged 33, was admitted to The Mount Sinai Hospital 3 times in the last year of his life. On the first admission he complained of headache and vomiting. He was found to have blood pressure of 232/144 mm., hypertensive neuroretinopathy and marked albuminuria. His symptoms improved and he was discharged. He was admitted again 3 months later for the same symptoms, as well as blurring of vision. This stay lasted 6 weeks.

* This patient was in The Jewish Hospital of Brooklyn, under the care of Dr. M. A. Rabinowitz, to whom we are greatly indebted for his courtesy in allowing us to report the case.

Six months later he was admitted for the third time. Fifteen days before he had noted dyspnea, which soon developed into severe orthopnea. On physical examination, there was slight puffiness of the ankles. The heart was enlarged to the left, the rate was rapid and gallop rhythm was present. Medium-sized moist râles were audible over both lower lobes. The liver was not palpable but percussion indicated slight enlargement. Arterial pressure was 210/150 mm. Venous pressure was 8.5 cm. Roentgenographic examination revealed intense engorgement and distention of the pulmonary vessels (Fig. 2). The non-protein nitrogen of the blood was 86 mg. %.

Three days after admission it was noted that *the patient was hoarse and laryngoscopic examination revealed left abductor paralysis*. This persisted until the death of the patient.

Two weeks after admission a pericardial friction rub was heard. Other manifestations of uremia appeared and the patient succumbed about 6 weeks after admission.

Necropsy. The cut surfaces of the *lungs* were very wet and abundant frothy fluid exuded from the bronchi. The main branches of the pulmonary artery were somewhat dilated and the walls were slightly thickened.

Heart: the *pericardial cavity* contained about 5 ounces of serosanguineous fluid. Both the visceral and parietal layers of the pericardium were studded with plaques of fibrin. The right ventricle was slightly hypertrophied and dilated; the left markedly hypertrophied and dilated. The mitral and other valves showed no changes. The coronary arteries were moderately sclerotic without being narrowed.

The *kidneys* were granular, and microscopic examination revealed glomerulonephritis of long standing.

The *left vagus and recurrent laryngeal nerves* were followed. The latter was flattened where it passed between the arch of the aorta and the left pulmonary artery. We are indebted to Dr. J. H. Globus for the following results of the microscopic examination:

Left vagus nerve proximal to the origin of the recurrent laryngeal nerve: Paraffin sections stained with hematoxylin and eosin showed no significant changes. Celloidin sections stained by the Marchi method failed to reveal myelin degeneration. Frozen section stained with Sudan III and hematoxylin showed fat in the connective tissue about the nerve but no fat droplet replacement of myelin within the nerve trunk. In the perineural tissues several medium-sized arteries were atherosclerotic.

Left recurrent laryngeal nerve where it passes between the arch of the aorta and the left pulmonary artery: Paraffin sections stained with hematoxylin and eosin were negative, as was the Marchi section. Frozen sections stained with Sudan III and hematoxylin showed fat droplets in ring formation about a few intact axis cylinders.

Left recurrent laryngeal nerve distal to the preceding: Paraffin sections stained with hematoxylin and eosin showed areas of vacuolization of myelin. Sections stained by the Marchi method revealed definite myelin degeneration with fat droplet replacement. Frozen sections stained with Sudan III and hematoxylin confirmed the finding by the Marchi method; fat droplets were seen surrounding many axis cylinders.

Left vagus nerve distal to the origin of the recurrent laryngeal nerve: Paraffin sections stained with hematoxylin and eosin, Marchi sections and frozen sections stained with Sudan III and hematoxylin did not show significant changes.

Sections from the above locations stained by the Weigert method revealed no changes sufficient to warrant deductions.

Summary of the Histologic Findings. The maximum degenerative change, as evidenced by myelin degeneration and fat droplet replacement is present

in the section taken from the left recurrent laryngeal nerve distal to the point where it passes between the left branch of the pulmonary artery and the arch of the aorta. The vagus nerve shows no significant changes.

Discussion. In each of the 3 cases described, the development of left ventricular failure, due to hypertensive and arteriosclerotic heart disease, was followed by paralysis of the left recurrent laryngeal nerve. This sequence of events suggests that the damage to the nerve is a result of the left ventricular failure, a conception which is fortified by the absence in the 2 cases that came to necropsy of any other cause for recurrent laryngeal palsy.

The mechanism by which injury to the left recurrent laryngeal nerve results from left ventricular failure can, perhaps, be most readily elucidated in the light of what is known about the pathogenesis of the same paralysis in mitral stenosis. By investigations on thoraces hardened *in situ* and *in toto*, Fetterolf and Norris¹ have shown that left recurrent laryngeal palsy in mitral stenosis is due to compression of the nerve between the left pulmonary artery and the aorta or ductus arteriosus. The left recurrent nerve passes between the arch of the aorta and the left pulmonary artery in a situation in which the two vessels are very close to one another (4 mm. apart, according to Fetterolf and Norris); indeed, the nerve is even normally flattened as it hooks around the aorta. It is quite obvious that even comparatively slight dilatation of the pulmonary artery might readily result in compression of the nerve between the pulmonary artery and the aorta, both of which are comparatively firm structures in consequence of the blood-pressure within them. Of course, a prerequisite for such compression is that the nerve be so fixed that it cannot merely be displaced laterally as the pulmonary artery dilates. The ductus arteriosus probably plays an important part in producing the palsy in this very way, namely, by preventing displacement of the nerve to the right. As a result, the nerve is constricted in a triangle bounded by the arch of the aorta, the left pulmonary artery and the ductus arteriosus. Apparently, however, the anatomic conditions necessary for the compression of the nerve by the expansion of the pulmonary artery are fulfilled in only a small proportion of individuals, for recurrent laryngeal paralysis is an unusual complication of mitral stenosis.

Previous investigators have visualized the compression of the left recurrent laryngeal nerve in mitral stenosis as due to *anatomic* dilatation of the pulmonary artery. This has, indeed, been present in some of the cases but in others it has been equivocal or absent. However, it does not seem that such anatomic dilatation, which can be demonstrated at necropsy, is necessary for the compression of the nerve. There may very well be a so-called *dynamic* dilatation, due to high pressure within the vessel, and which is not evident at necropsy. How marked such dynamic dilatation of an artery

may be is familiar to clinicians from the fluoroscopic appearance of the aorta in many instances of aortic insufficiency. As a result of the large volume of blood ejected into the aorta by each systole in aortic insufficiency, the aorta may appear greatly dilated during life, but at necropsy its measurements do not exceed the normal. Similarly, roentgenographic examination in mitral stenosis reveals that the pulmonary artery and its first branches are greatly dilated and, as in the instance of aortic insufficiency, this dilatation may be largely or completely "dynamic;" at postmortem, the vessels in question are not correspondingly, if at all, dilated.

In the light of these facts, it seems probable that *functional* moments predominate in the compression of the left recurrent laryngeal nerve in mitral stenosis. As a result of the mitral obstruction, engorgement and hypertension of the lesser circulation develop. One of the consequences of the increased pressure is dynamic dilatation of the pulmonary artery and its branches. The development of the latter is facilitated by the great elasticity of the pulmonary artery and its first branches. It is true that if the hypertension of the pulmonary circulation is sufficiently protracted, arteriosclerosis, diminished elasticity and anatomical dilatation of the pulmonary artery may result. But such anatomical dilatation of the pulmonary artery is not always present when left recurrent laryngeal palsy complicates mitral stenosis.

In the 3 cases described above of left recurrent laryngeal palsy complicating hypertensive and arteriosclerotic heart disease, there is every reason to believe that the functional element of hypertension of the lesser circulation with resultant dynamic dilatation of the pulmonary artery was the cause of the compression of the nerve, just as in mitral stenosis. The evidence for this view is as follows:

1. In all the cases the recurrent laryngeal palsy *followed* the onset of left ventricular failure.

2. In Case 1 the left recurrent laryngeal nerve was definitely constricted and discolored for a length of 0.5 cm., where it passed through the triangle bounded by the arch of the aorta, the left pulmonary artery and the ductus arteriosus. In Case 3 the histologic findings also indicated compression at this point.

3. In Case 1 no significant "anatomic" dilatation of the pulmonary artery was demonstrable at necropsy; the aorta and the ductus arteriosus likewise exhibited no notable changes. In Case 3 the dilatation of the pulmonary artery found at necropsy was but minimal.

4. The evidences of engorgement and hypertension of the pulmonary circuit with dynamic dilatation of the pulmonary artery and its branches during life were clear-cut and unequivocal: (a) The pulmonic second sound was louder than the aortic second sound. (b) The chest films in Cases 1 and 3 revealed intense engorgement of the pulmonary vessels, the dilatation of the smaller radicles

being visible far out toward the periphery of the lung fields. We did not see the chest film of Case 2. (c) In Case 2 there were repeated attacks of massive pulmonary edema, while the other 2 patients had marked pulmonary edema at necropsy.

Summary. Three cases of left recurrent laryngeal palsy complicating hypertensive and arteriosclerotic heart disease with left ventricular failure are described. Two of the cases were instances of coronary thrombosis.

Evidence is presented that the left recurrent laryngeal palsy was due to compression of the nerve between the left pulmonary artery, the arch of the aorta and the ductus arteriosus. The cause of the compression is regarded as dynamic dilatation of the pulmonary artery due to the engorgement of the lesser circuit engendered by the failure of the left ventricle.

In the light of these cases and other evidence, it is suggested that when recurrent laryngeal paralysis complicates mitral stenosis, the *dynamic* dilatation due to the hypertension of the lesser circulation probably plays a significant part.

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LIMITATIONS OF AUSCULTATION FOR THE DIAGNOSIS AND STUDY OF TUBERCULOUS PULMONARY CAVITIES.

BY B. T. McMAHON, M.D.,

ASSOCIATE PHYSICIAN, LOOMIS SANATORIUM,

AND

EDMUND H. KERPER, M.D.,

ROENTGENOLOGIST, LOOMIS SANATORIUM, LOOMIS, N. Y.

THE following observations of the limitations of auscultation were made in connection with a study of the healing of tuberculous pulmonary cavities.¹ The series consisted of 296 cases of pulmonary tuberculosis with cavity and with tubercle bacilli in the sputum; the total number of cavities estimated from roentgenograms was 464. All patients were examined once a month and stereoscopic Roentgen ray films were taken on an average of every 2 months. Correlation was thus possible between stethoscopic findings and Roentgen ray interpretations, both in regard to the presence of cavity signs and alterations in cavity dimensions. Elicitation of any one of the usual textbook physical signs of cavity was sufficient to lead the examiner to suspect its presence, while more than one strengthened the likelihood. Patients with so-called "silent cavities,"

i. e., cavities visualized in the roentgenogram but not suspected on physical examination, were reexamined to make certain that cavity signs were not overlooked. Particular attention was given to the area of distribution and character of râles. Whenever significant changes in the lesion were noticed in the serial Roentgen ray films, correlation was made with the physical examination for that time, especially as to changes in râles.

Cavity was diagnosed by physical examination in 119 (40%) of the 296 cases. This figure refers to cavity-bearing areas, containing either single or multiple cavities. In a separate study of 170 cases with solitary cavity, a diagnosis of cavity was made in only 53 (31%). Here size was a factor, because the percentage of positive diagnoses increased from 21% for cavities of dimensions not over 2 by 2 cm. to 53% for cavities over 4 by 4 cm. It was likewise true that fresh, thin-walled cavities were more easily missed than those with fibrous walls or surrounding consolidation.

To determine how accurately changes in râles indicated mutations in pathologic anatomy as portrayed by Roentgen ray, two large contrasting groups of the original study¹ were examined. The first group comprised 65 cases that secured spontaneous closure of cavity, the criteria for which were the disappearance of shadows representing cavity in serial Roentgen rays and the absence of tubercle bacilli from the previously positive sputum for at least 3 consecutive months. The second group comprised 84 cases in which the size of the cavities at the end of treatment was the same or larger.

Of the group that secured spontaneous closure of cavity, râles were unaltered after closure in 30.8%, diminished in 67.7% and increased in 1.5%. Of the second group, finally classified as unimproved, râles were increased in 40.4%, unchanged in 47.6% and diminished in 11.9%. Consequently, estimation of changes in cavities deduced from variations in râles is unreliable, since râles may increase or remain the same while the lesion heals, or they may diminish while the lesion is stationary or progressive.

While this experience demonstrates that auscultation has its limitations in the diagnosis of pulmonary cavities and in the detection of changes during healing or enlargement, it must not be assumed that Roentgen ray interpretation is infallible. Many intrapulmonary lesions cast shadows on the roentgenogram indistinguishable from tuberculosis and small tuberculous lesions cannot be clearly shown, especially if Roentgen ray technique is not the best. Furthermore, such conditions as pleural friction, pulmonary edema, bronchitis, and sometimes emphysema can be more readily detected by auscultation than by Roentgen ray. Treating tuberculosis on the basis of Roentgen ray alone overlooks the importance of other clinical features and of personality as a guide to treatment

and prognosis. For this purpose a well-taken history and a careful physical examination are indispensable.

Summary and Conclusions. If reliance had been placed on auscultation alone in this series of 296 cases of cavitary tuberculosis, only half the large cavities diagnosable by Roentgen ray would have been detected and 4 out of 5 of the smaller ones would have been missed. In practice, it is therefore wise to withhold final opinion on the presence or size of cavity until the Roentgen film has been read. Roentgenograms and fluoroscopic examinations at intervals of weeks or months are the best means at our command of observing the behavior of cavities as to size and character. For this purpose deductions made from changes in extent, character, and number of râles are unreliable, since râles may increase or remain the same as the disease heals or they may diminish as the disease grows worse.

Recognition of these limitations of auscultation leads to greater accuracy in diagnosis and emphasizes the need for correlation of physical, Roentgen ray and laboratory examinations.

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SOME EFFECTS OF QUININ DERIVATIVES IN EXPERIMENTAL PNEUMOCOCCUS STUDIES.*

By W. W. G. MACLACHLAN, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, UNIVERSITY OF PITTSBURGH; PHYSICIAN TO THE
MERCY HOSPITAL,

H. H. PERMAR, M.D.,

ASSOCIATE PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH; DIRECTOR OF
LABORATORIES, MERCY HOSPITAL,

JOHN M. JOHNSTON, A.B., M.D.,

INSTRUCTOR IN MEDICINE, UNIVERSITY OF PITTSBURGH; ASSISTANT IN MEDICINE,
MERCY HOSPITAL,

AND

JOSEPH R. KENNEY, A.B., B.S., M.D.,

DEMONSTRATOR IN MEDICINE, UNIVERSITY OF PITTSBURGH; ASSISTANT IN MEDICINE,
MERCY HOSPITAL, PITTSBURGH, PA.

(From the laboratories of the Mercy Hospital.)

IN this article we are reporting the results of a study of certain quinin derivatives with reference to their power to destroy the pneumococcus in the test tube and to protect mice which have been

* Read at the meeting of the Association of American Physicians at Atlantic City, May 1, 1934.

inoculated by an intraperitoneal injection of pneumococci.* The clinical results in a few cases which we have treated with the ethylapoquinin made at the Mellon Institute have been very satisfactory, but a much larger series of cases must be studied as a basis for conclusions. Type II pneumococcus was used, although we have made observations, as have others, to indicate that all pneumococci are affected equally by the quinin derivatives. Also, the toxicity of the derivatives was estimated by intraperitoneal injection in mice. We have examined 35 different preparations of the quinin group (21 various salts as given below, 12 different preparations of ethylapoquinin and 1 each of hydroxyethylapoquinin and hydroxyethylhydrocuprein); of these we have excluded, as being of little value for their slight antipneumococcic power, all but 3. The 3 which we have studied in detail are ethylapoquinin, hydroxyethylapoquinin and hydroxyethylhydrocuprein. Ethylhydrocuprein (optochin) was used in practically all of our experiments at the same time, naturally as a control quinin derivative of which the action on the pneumococcus and the toxicity are well known.

Ethylapoquinin was discovered, in 1895, in Germany, by Lippmann and Fleissner.¹ In 1930, Miura and Okamoto,² in Japan, noted that it had greater bacteriocidal power for the pneumococcus in the test tube, gave more protection to mice inoculated with pneumococcus and was less toxic than optochin. In the following year, Miura and Sogen,³ and Okamoto⁴ confirmed this work. In 1931, Osato and Watanabe⁵ reported some observations on 10 cases of influenzal pneumonia—the only clinical report on the use of ethylapoquinin of which we are aware. The authors were impressed with the results noted in the small group of cases. Two of the patients died, but 1 was apparently a terminal case at the onset of the treatment. The dosage was 1.5 gm. of the base or 1 gm. of the hydrochlorid in divided doses for the 24-hour period. It was continued for 3 or 4 days. One fatal case was given, 7.5 gm. in 5 days. One of the patients had a transitory blindness for a few days. From reading this report, one cannot really estimate the severity of the infection of the cases, for no observations were made as to the presence of pneumococci in the blood stream as indicated by positive blood cultures. The dosage of the drug was the same as has been recommended for optochin and it is of interest that one example of visual disturbance was noted. In 1933, Gundel and Seitz,⁶ in Germany, confirmed the findings of Miura and Okamoto.

Hydroxyethylapoquinin and hydroxyethylhydrocuprein are new derivatives made at the Mellon Institute.

* In this work we were associated with Drs. L. H. Cretcher, C. L. Butler and A. G. Renfrew, of the Department of Research in Pure Chemistry of the Mellon Institute. They will make a separate report on the chemical phases of the preparations. We wish to thank also Prof. W. T. Dawson, of the University of Texas, for assistance.

The bacteriocidal action of the various quinin derivatives on the pneumococcus was carried out in the following way: 0.1 cc. of a 1 to 1000 dilution of an 18-hour broth culture was added to a dextrose broth which contained the quinin derivative in the proper dilution. At the end of 2, 4, 6, 10 and 24 hours, blood-agar plates were streaked with a standard loop from the broth and the colonies of pneumococci were counted in 24 hours. It is well known that the quinin derivatives vary greatly in their bacteriocidal action on the pneumococcus *in vitro*. We used optochin as the control drug, and only those preparations which equalled optochin in their bacteriocidal power were further studied, except in 1 instance, hydroxyethylhydrocuprein, which was definitely lower. The *in vitro* tests, therefore, were used more to exclude the weaker preparations in antipneumococci power than to attempt to accurately define the maximum bacteriocidal dilutions of each derivative. Chart I gives the end results of this part of our work. Any one of several specimens of ethylapoquinin showed the same bacteriocidal effect in the dilution stated. Chart II shows a fairly typical curve of the bacterial count for one of the ethylapoquinins and hydroxyethylhydrocuprein. Fresh solutions of the quinin derivatives were always used as the bacteriocidal power for pneumococcus is lowered if the diluted solutions are allowed to stand for a few days.

The other quinin derivatives, which we have tested and discarded on account of their lesser bacteriocidal power for the pneumococcus, were as follows:

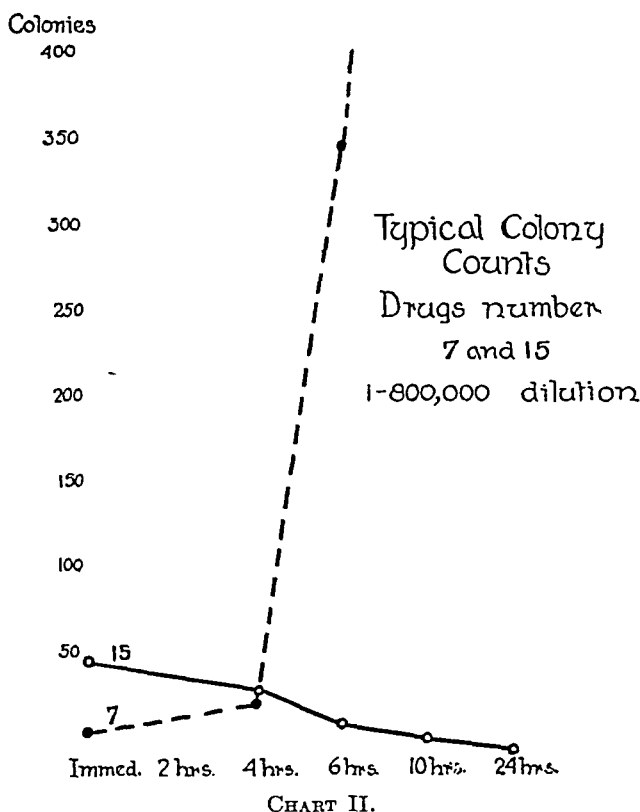
- | | |
|---------------------------------------|---|
| 1. Quinin sulphate (neutral) | 13. a. Hydroquinin dihydrochlorid |
| 2. Quinidin sulphate (neutral) | 14. Epihydroquinidin dihydrochlorid |
| 3. Cinchonin sulphate (neutral) | 16. Hydroxydihydroquinin dihydrochlorid |
| 4. Cinchonidin hydrochlorid (neutral) | 19. Isoquinin dihydrochlorid (?) |
| 5. Epiquinin dihydrochlorid | 20. Cl-ethylhydrocuprein dihydrochlorid |
| 6. Epiquinidin dihydrochlorid | 28. Niquin dihydrochlorid |
| 8. Hydroquinin neutral sulphate | 29. Ethyleuprein dihydrochlorid |
| 9. Quitenin hydrochlorid | 33. Vinylhydrocuprein dihydrochlorid |
| 10. Ethylquitenin hydrochlorid | 34. Ethoxyethyl hydrocuprein dihydrochlorid |
| 11. Quitenidin | |
| 12. Hydroquinon hydrochlorid | |
| 13. Hydroquinin neutral sulphate | |

CHART I.—PNEUMOCOCCIDAL POWER IN VITRO.

Drug.	No.	Killed pneumococci in
Ethylhydrocuprein . . .	0	1 to 800,000 dil.
Hydroxyethylhydrocuprein . .	7	1 to 200,000 "
Ethylapoquinin . . .	15, 22, 23, 26, 31, 32	1 to 800,000 "
Hydroxyethylapoquinin . .	30	1 to 800,000 "

The estimation of the toxicity of the quinin derivative was carried out on mice by injection intraperitoneally of doses, ranging from 2 to 7 mg. If death occurred, it almost invariably happened in from 5 to 30 minutes. Animals surviving $\frac{3}{4}$ hour practically always lived. The toxicity experiments were also used as a method to eliminate some of the preparations, as it was useless to proceed with highly toxic

derivatives. In these experiments we used optochin as a control quinin derivative. Chart III brings out two interesting points in reference to toxicity: (1) There is a considerable variation in the different preparations of ethylapoquinin. We have been able to compare samples made in Japan, in Germany and at the Mellon Institute. (2) All of the preparations of ethylapoquinin which we have examined showing a levorotatory power of 180 or less were very toxic and as the optical activity rose above -200 , toxicity definitely decreased. Cretcher⁷ has pointed to this fact as being of great practical value in the preparation of this compound. On the other hand, the actual



level of the levorotatory power does not necessarily indicate the relative degree of toxicity as Chart III shows in the last two numbers, 15 and 31. This chart also shows in preparations 23 and 26, which represent a fairly pure end product, how earlier fractions of the same preparations varied in their toxicity as noted in 18 and 22 (for end product 23) and 24, 25 and 27 (for end product 26). In Chart III only 10 mice were used for the toxic fractions as indicated in derivatives numbered 18 and 22; in 25, 26 and 27. There is probably an inaccuracy in Chart III which shows 23 at 2 mg. (15 mice) with a higher level of death than 23 at 3 mg. (30 mice). The

error of determination of toxicity is of course less with 30 animals than with 10 or 15 in a group.⁸ In all the other columns 30 mice were used.

Chart IV shows the relative toxicity of the quinin derivatives. It is to be noted that the ethylapoquinins vary appreciably. Prepa-

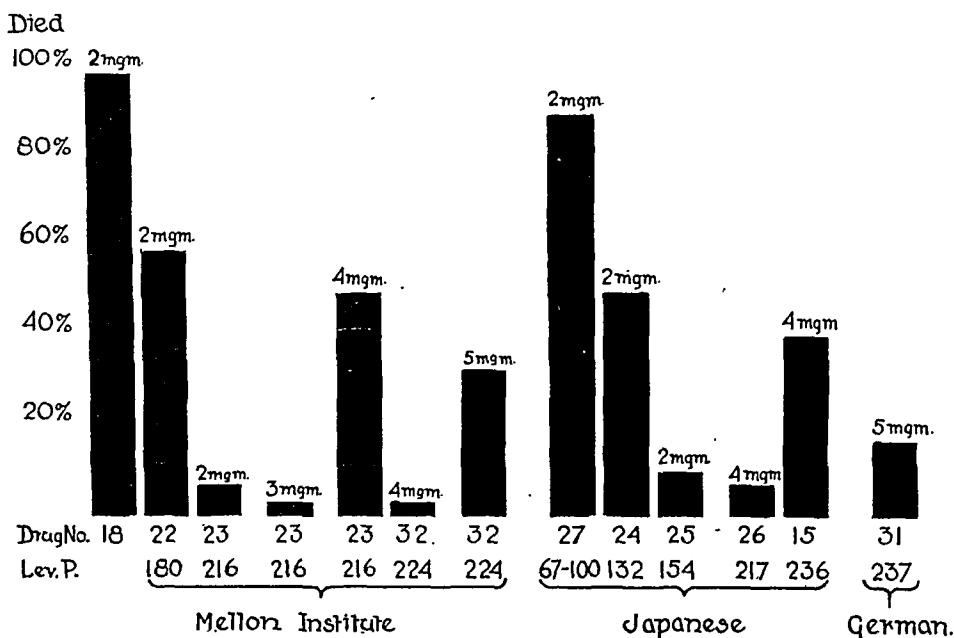


CHART III.—Comparative toxicity of various preparations of ethylapoquinin—dihydrochlorid.

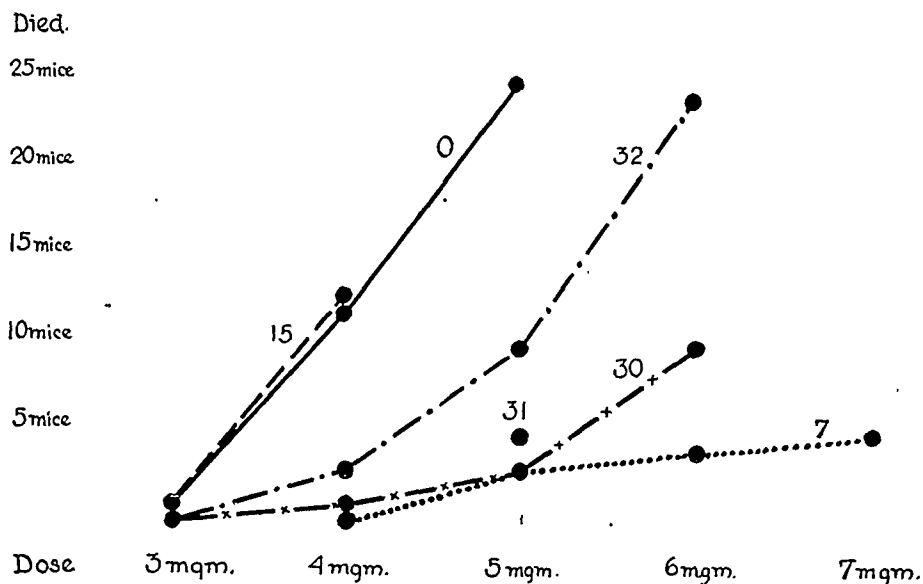


CHART IV.—Comparative toxicity of the hydrochlorids of ethylhydrocuprein (0), hydroxyethylhydrocuprein (7), ethylapoquinin (15), (31), (32), hydroxyethylapoquinin (30).

ration 15 (Japan) is more toxic than 32 (Mellon Institute), while 31 (Germany) is slightly less toxic but also slightly less protective (Chart V) than 32. Of greater interest to us was the curve of hydroxyethylapoquinin, 30. This derivative is less toxic than any ethylapoquinin studied. Finally in hydroxyethylhydrocuprein, 7, we have the least toxic of all derivatives that we have examined.

Lived

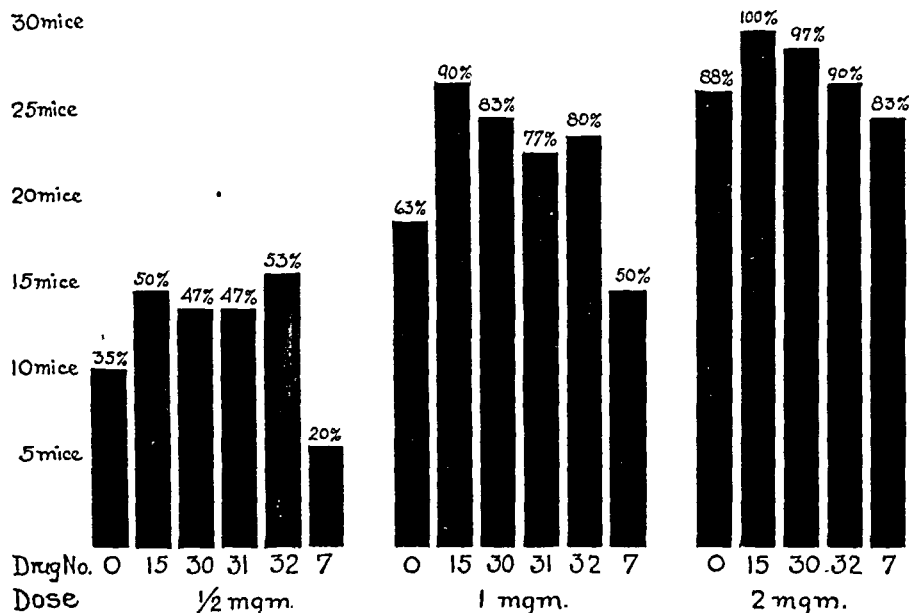


CHART V.—Comparative protective power of the hydrochlorids of ethylhydrocuprein (0), ethylapoquinin (15), (31), (32), hydroxyethylhydrocuprein (7), hydroxyethylapoquinin (30).

The protection of mice against intraperitoneal injections of pneumococci was carried out in the following manner: 0.1 cc. of an 18-hour broth culture of pneumococcus, which in the same quantity in a dilution of 1 to 1000 would kill 20- to 22-gm. mice in from 16 to 20 hours, was injected into the peritoneal cavity. This dose is, therefore, 1000 times the lethal dose. One half hour after the injection, the quinin derivative was given intraperitoneally in 3 different dosages, namely, 0.5 mg., 1 mg. and 2 mg. In each series of protective experiments for each dose 30 mice were used, but as optochin was used as a control drug in all protective tests, except with 31, each dark column for optochin represents 60 mice. Further for each group of 30 mice in all of the protection tests, 6 controls were used, and of this number, 120 in all, only 5 failed to die. Chart V indicates that ethylapoquinin is superior to optochin in protection more definitely noted in the smaller doses, 0.5 and 1 mg.

The different ethylapoquinins also vary a little in their protective power. Hydroxyethylapoquinin appears to be more powerful than ethylapoquinin except 15, which is, however, the most toxic ethylapoquinin. Hydroxyethylhydrocuprein lags somewhat in its protective power, except in the large dose of 2 mg., where the difference is not great.

Summary. Our work, therefore, confirms what Miura and Okamoto stated in reference to the superior protective power of ethylapoquinin over optochin in experimental pneumococcus infection of mice. We have noted that ethylapoquinin varies considerably in its toxicity depending upon its chemical purity. The lessened toxicity fortunately does not diminish its protective power. Clearly these variations in the different samples of ethylapoquinin must be taken into consideration in interpreting the results of experimentation, and most decidedly this must be remembered if later this derivative is to be used clinically. It is noteworthy that the estimation of the degree of levorotatory power in ethylapoquinin has been of value as a physical test for the toxicity of the derivative. The chemists believe that this physical property will be of great aid in the actual preparation of this substance, which can be very toxic in its action on animals if impure.

Of the two new derivatives, hydroxyethylapoquinin is the more important. This preparation has less toxicity than any of the ethylapoquinins and greater antipneumococcic power than any of them except 15. According to our data the latter preparation (15) was as toxic as optochin. The low toxicity of hydroxyethylapoquinin combined with its high protective power as indicated by the experimental results show it to be superior to the ethylapoquinins. Hydroxyethylhydrocuprein is the least toxic and although its protective action is not as great as any of the other derivatives described above, yet its low toxicity makes this compound of definite interest.

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THE DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF THE
CREATIN-CREATININ METABOLISM IN VARIOUS MYOP-
ATHIES BEFORE AND AFTER AMINO-ACID THERAPY.*

By HOWARD H. BEARD, M.A., PH.D.,
PROFESSOR OF BIOCHEMISTRY,

CARLO J. TRIPOLI, M.D.,
INSTRUCTOR IN MEDICINE; SENIOR HOUSE PHYSICIAN,

AND

JEROME E. ANDES, PH.D.,
INSTRUCTOR IN BIOCHEMISTRY,
LOUISIANA STATE UNIVERSITY MEDICAL CENTER, AND THE STATE CHARITY HOSPITAL,
NEW ORLEANS, LA.

SINCE the introduction of amino-acid therapy in the treatment of muscular dystrophies and atrophies, conflicting reports have appeared in the literature. A review of our treated cases and those of other workers¹ shows that studies on creatin-creatinin metabolism have been made which we believe important. It may be somewhat difficult for the clinician to distinguish between the myopathies due to abiotrophic changes in the muscles themselves and those due to nerve injury. Also there are no definite criteria by which to predict the results in any given case before amino-acid therapy is begun or after its administration over a short period of time. There are several factors which may influence the prognosis in a given case. These are the type and duration of the disease, the age of the patient, coëxisting infections and other systemic diseases and the amount of functional muscle tissue remaining in the patient. Our review of the results achieved leads us to believe that, after consideration of these factors, a study of creatinuria may prove a real aid in the early diagnosis and prediction of the therapeutic result possible in a particular case.

Direct chemical and histologic studies of the diseased muscles before and after amino-acid therapy may also yield information of much prognostic value. Such studies have been made by Tripoli and Beard,¹ Milhorat² and by Reinhold and coworkers.³ The latter investigators showed that, in cases of advanced muscular dystrophy, a reduction in the concentration of various muscular constituents to about 5 or 10% of their normal value occurred, while in earlier cases this reduction amounted to but 50% of the normal value. Most conspicuous was the reduction in the creatin content of the muscle. After glycin therapy a restoration of the muscle constitu-

* A preliminary report of these studies was presented before the Biochemical Division of the American Chemical Society at the 87th meeting, St. Petersburg, Fla., March 27, 1934.

ents took place, especially of total nitrogen and of creatin. Histo-logic studies were in accord with these chemical findings.

We wish to present in this paper our observations on creatin-creatinin metabolism in 30 of our cases,^{1,4} with especial reference to the relationship between the creatinuria and the diagnosis and prognosis following the institution of amino-acid therapy.

Methods. The daily excretion of total creatinin, preformed creatinin and creatin in the urine was studied during a control period of 5 days. At the end of this time from 10 to 15 gm. of glycine or glutamic acid were given daily in water, milk or fruit juice. No change was made in the usual diet of the patients. The effect of this treatment upon the excretion of the creatin bodies was studied in 24-hour specimens of urine for 3 similar periods of 5 days each. Total creatinin was determined by the method of Benedict and Myers⁵ and preformed creatinin by the method of Folin.⁶ The daily excretion of total creatinin minus the excretion of the preformed creatinin times 1.16 is equivalent to the daily creatin output.

TABLE 1.—CREATIN-CREATININ METABOLISM IN VARIOUS MYOPATHIES AFTER AMINO-ACID THERAPY. (AVERAGE 24-HOUR EXCRETION IN DIFFERENT PERIODS.) (AVERAGE VALUES FOR EACH GROUP.) (BEARD, ANDES AND TRIPOLI.)

Patient No.	Age, years.	Control period.			Amino acid, 10-15 gm. daily.	First period.			Second period.			Third period.		
		Total creatinin	Preformed creatinin	Creatin		Total creatinin	Preformed creatinin	Creatin	Total creatinin	Preformed creatinin	Creatin	Total creatinin	Preformed creatinin	Creatin
		gm.	gm.	gm.		gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.
Group 1 1-10*	8-37	1.17	0.73	0.50	Glutamic acid or glycine	1.38	0.72	0.77	1.16	0.56	0.10	1.14	0.65	0.57
					% Increase	18.0	None	54.0	None	None	40.0	None	None	16.0
Group 2 11-17†	12-54	1.15	0.82	0.38	Glutamic acid or glycine	1.72	1.08	0.74	1.38	0.99	0.45	0.97	0.81	0.18
					% Increase	49.5	32.9	94.7	20.0	20.7	15.8	None	None	None
Group 3 18-30‡	7-55	1.49	0.94	0.64	Glutamic acid or glycine	1.64	1.07	0.66	1.53	1.08	0.52	1.32	0.92	0.46
					% Increase	10.0	13.8	None	2.7	14.9	None	None	None	None

RESULTS.—Group 1, objective and subjective improvement; Group 2, subjective improvement; Group 3, no improvement.

* Cases 1 to 10 were: Pseudohypertrophic muscular dystrophy, 4; progressive muscular dystrophy, 3; and 1 each of "Psychopathic inferiority complex" (disuse atrophy), early spinomuscular atrophy and strabismus.

† Cases 11 to 17 were: Amyotrophic lateral sclerosis, 4; and 1 each of hypothyroid-hypopituitary, multiple sclerosis and spinomuscular dystrophy.

‡ Cases 18 to 30 were: Pseudohypertrophic muscular dystrophy, 3; progressive spinomuscular atrophy, 2; poliomyelitis, 2; and 1 each of "Friedreich's ataxia," tabes dorsalis with muscular dystrophy, muscular atrophy following radial nerve injury, von Recklinghausen's disease, "Jamaica ginger paralysis" and paresis with muscular atrophy.

Results and Discussion. The average results obtained are listed in Table 1. For purposes of comparison we may divide the cases into 3 groups, as follows:

GROUP 1 (Cases 1 to 10). Patients in whom the average creatin excretion rose from 50 to 200% above that of the control period

(provided this increased creatinuria soon disappeared in the third or subsequent period), showed both subjective and objective improvement. Cases 8 and 10 were the exceptions. In the latter the amino-acid therapy apparently helped the patient to retain the large amount of creatin excreted daily.

GROUP 2 (Cases 11 to 17). Some neuromuscular patients, who showed about the same degree of increase and decrease in creatinuria as those of Group 1, showed only subjective improvement or had arrest of progress of their clinical symptoms.

GROUP 3 (Cases 18 to 30). Patients in which no increased creatinuria occurred, or where it was less than 50% above that observed in the control period, showed no improvement. Exceptions were Cases 18 and 25.

The correlation of the increased creatinuria with clinical improvement is further shown in the observations of other investigators^{2,9,10,11,12} in this field (Table 2).

TABLE 2.—THE PROGNOSTIC SIGNIFICANCE OF CREATINURIA IN CASES OF VARIOUS MYOPATHIES DURING AMINO-ACID THERAPY. (COMBINED RESULTS OF OTHER AUTHORS.)

Myopathy.	No. of cases.	Creatin-urea.	Clinical results.	Observer.
Progressive muscular dystrophy	3	++	Marked improvement	Milhorat, Techner and Thomas. ¹⁰
Progressive muscular dystrophy	14	++	Marked improvement	Milhorat. ²
Progressive muscular dystrophy	7	++	Good improvement	Kostakow and Slauck. ¹¹
Pseudohypertrophic muscular atrophy	3	++	Marked improvement	Milhorat, Techner and Thomas. ¹⁰
Myasthenia gravis	20	+++	Marked improvement	Boothby. ⁹
Pseudohypertrophic muscular dystrophy	2	++	Good improvement	Mettel and Slocum. ¹²

Creatin Excretion. The average variation of the creatinuria before amino-acid therapy was from 0.07 to 1.63 gm. in the 17 cases which improved or in which the progress of the disease had been arrested. In the remaining 13 cases which showed no improvement the average creatin excretion varied from 0.0 to 1.43 gm. Thus the degree of initial creatinuria seems to bear little relation to the subsequent clinical improvement in the patient after amino-acid therapy.

Most of our patients who improved showed an excellent ability to form creatin from the amino acids. This confirms the fact that the metabolic fault of the myopathy patient is not the inability to form creatin, but an inability to retain and utilize the creatin in the muscles. A subsequent disappearance of the creatinuria and

storage of creatin in the muscles is then associated with clinical improvement.

It is significant from the diagnostic and prognostic points of view that no increased creatinuria (above 50% of that of the control period) after amino-acid therapy was observed in Cases 18 to 30, most of which were suffering from neuromuscular conditions. This evidently indicates that the lower motor neurone (trophic unit) with the muscle it innervates is necessary, not only for the functional activity of the muscle, but also for creatin formation from amino acids. We believe that this lack of increased creatinuria after amino-acid therapy may prove to be a real aid in distinguishing the neuromuscular conditions from the muscular dystrophies. Possibly this fact may also explain why very little, if any, objective improvement is to be expected in these neuromuscular conditions, whereas in the muscular dystrophies and particularly in cases of myasthenia gravis which are probably primarily muscular conditions, objective improvement may and does occur after amino-acid therapy. If the above reasoning is correct, it would seem that, from the metabolic point of view, the 4 cases of amyotrophic lateral sclerosis (Cases 11 to 14) would stand midway between the dystrophies and the other neuromuscular conditions, even though they are muscular diseases due to lesions in the central nervous system. In these cases increased creatin formation and excretion were associated with only subjective improvement.

Harris and Brand⁷ stated that their patients with muscular dystrophy usually excreted larger amounts of creatin than comparable patients suffering from neuromuscular conditions. The average creatin excretion of our first 10 cases suffering from dystrophies was 0.50 gm.; in the 15 neuromuscular cases it was 0.73 gm. Thus the initial creatinuria in both types of diseases was about the same.

Adams,⁸ in a preliminary paper, stated that the increase in creatin after glycine therapy appears to be proportional to the degree of creatinuria before glycine is administered. The creatin excretion, before amino-acid therapy in the 30 cases reported in this paper, was practically constant from day to day in 20 patients, while in the remaining 10 it varied from 50 to 200%. The data for our 16 cases which showed subjective and objective improvement show that the ability of the patient to form, utilize, or excrete creatin is probably not necessarily dependent upon the degree of his creatinuria before amino-acid therapy is begun, but rather upon the degree of increased and decreased creatinuria after the therapy is instituted.

Creatinin Excretion. The average variation in the daily preformed creatinin excretion before amino-acid therapy was from 0.15 gm. to 1.69 gm. Accepting 1.50 gm. as about the normal daily creatinin excretion we had 5 patients who excreted from 1.50 to 1.70 gm.; 6 from 1 to 1.50 gm. and 19 below 1 gm. The

average daily amount excreted by all patients was 0.85 gm. This confirms the well-known fact that the creatinin excretion is below normal in different types of myopathies. In 18 patients the daily creatinin excretion was practically constant, while in 12 patients it varied from 0.15 to 1.30 gm.

It is generally believed that the creatinin output is not affected in the myopathies after amino-acid therapy. Our previous results and those of several others^{13,14} show definitely that the creatinin output can be increased in normal animals and man, as well as in the myopathies after amino-acid therapy. In 15 patients reported in this paper the creatinin excretion increased from 11 to 67% above that of the control period after amino-acid therapy. This affords additional evidence of the exogenous origin of creatinin from the amino acids of the diet.

TABLE 3.—THE EFFECT OF AMINO-ACID INGESTION UPON THE DISTRIBUTION OF NITROGEN IN THE URINE IN DIFFERENT MYOPATHIES. AVERAGE VALUES.

	Substance.	Control period.			First period.			Second period.			Third period.		
		Amount, gm.	Nitrogen content.	Per cent of total N.	Amount, gm.	Nitrogen content.	Per cent of total N.	Amount, gm.	Nitrogen content.	Per cent of total N.	Amount, gm.	Nitrogen content.	Per cent of total N.
B Amyotrophic lateral sclerosis	Total N	...	14.40	17.55	15.13	14.03	...
	Urea	25.59	11.93	82.4	31.61	14.74	84.0	27.46	12.81	84.7	24.97	11.65	82.9
	Ammonia	0.90	0.74	5.1	1.01	0.84	4.8	0.80	0.66	4.4	0.77	0.61	4.6
	Uric acid	0.55	0.18	1.3	0.61	0.20	1.2	0.47	0.16	1.0	0.41	0.14	1.0
	Creatinin	1.55	0.57	4.0	2.08	0.77	4.5	1.87	0.69	4.6	1.78	0.66	4.7
	Creatin	0.56	0.18	1.3	0.91	0.31	1.7	0.17	0.06	0.3	0.18	0.20	1.4
	Undetermined N by difference	...	0.79	5.8	...	0.70	4.0	...	0.75	4.9	...	0.75	5.4
G Tabes dorsalis	Total N	...	10.71	11.08	10.62	9.98	...
	Urea	18.22	8.51	79.4	18.98	8.85	79.6	18.65	8.70	81.9	17.33	8.08	81.0
	Ammonia	0.68	0.58	5.2	0.48	0.37	5.4	0.60	0.49	4.6	0.50	0.41	4.1
	Uric acid	0.47	0.15	1.8	0.49	0.16	1.4	0.39	0.13	1.2	0.33	0.11	0.9
	Creatinin	1.42	0.56	5.3	1.56	0.60	5.3	1.47	0.54	5.1	1.30	0.49	4.9
	Creatin	0.98	0.31	2.4	0.30	0.10	0.8	0.73	0.24	2.3	0.11	0.03	0.3
	Undetermined N by difference	...	0.63	5.7	...	0.79	7.2	...	0.52	4.8	...	0.86	8.6
G Progressive muscular dystrophy	Total N	...	7.73	8.53	8.55	8.30	...
	Urea	12.49	5.83	74.9	14.05	6.55	76.6	14.40	6.73	78.5	14.50	6.76	81.2
	Ammonia	0.68	0.57	7.4	0.90	0.74	8.9	0.79	0.65	7.6	0.67	0.55	6.8
	Uric acid	0.34	0.12	1.5	0.36	0.12	0.1	0.37	0.18	1.4	0.33	0.11	1.3
	Creatinin	0.58	0.22	2.8	0.46	0.17	2.1	0.45	0.20	2.0	0.45	0.17	2.2
	Creatin	1.09	0.34	4.3	0.68	0.21	2.5	0.76	0.25	2.8	0.65	0.21	2.4
	Undetermined N by difference	...	0.67	8.9	...	0.72	8.4	...	0.54	7.4	...	0.48	6.9

In 3 of our cases we made a study of the effect of amino-acid ingestion upon the distribution of nitrogen in the urine in the form of total, urea, ammonia, uric acid, creatin, creatinin and undetermined nitrogen (Table 3). There was no significant change during the first period after amino-acid ingestion in the excretion of the total, urea, ammonia and uric acid nitrogen in the 3 cases, with the possible exception of a slight rise in the first period in the total and urea nitrogen in the case of amyotrophic lateral sclerosis. In

this case there was also an increase of 45 % in creatin excretion which later disappeared. The increase in creatinin excretion was 40, 26 and 17 % greater in the 3 experimental periods than it was in the control period. In the case of *tabes dorsalis* there was a 32 % increase in creatin excretion in the first experimental period with no corresponding increase in creatinin excretion. In case of progressive pseudohypertrophic muscular dystrophy there was no increased creatin or creatinin excretion. These results are in accord with the observations of Adams,⁸ who observed that in a case of myasthenia gravis no significant changes occurred in nitrogen, phosphorus or sulphur balance after amino-acid ingestion.

It is significant here that in 1 case there was an increased creatinin output with no corresponding change in excretion of other nitrogenous substances, while in the other 2 cases, despite the increased amino-acid intake, no corresponding increase in different forms of nitrogen was noted. This observation in the latter 2 cases may be explained by a lack of amino-acid absorption or a defect in protein metabolism, as evidenced by the work of other investigators.³ Further studies in this direction are contemplated.

Our studies confirm and extend those of Milhorat,² who observed increased creatinuria after glycine administration in cases of muscular dystrophy but not in cases of secondary muscular atrophy. Milhorat pointed out that glycine was helpful in the differential diagnosis between the primary myopathies and secondary degenerations.

Summary. The creatin and creatinin excretion in the urine of 30 of our 46 patients suffering from various myopathies has been studied before and after the institution of amino-acid therapy.

Both subjective and objective clinical improvement were observed in 10 patients and subjective improvement only in 7 patients whose creatin excretion rose from 50 to 200 % above that of the control period, provided this increased creatinuria soon disappeared or returned to the control level. In 4 other cases, the progress of the disease was arrested.

No clinical improvement took place in 13 cases, 9 of which were suffering from neuromuscular conditions, in which increased creatinuria was absent or less than 50 % above that of the control period.

The possible diagnostic and prognostic significance of these creatinuria studies in the myopathies treated with amino acids is discussed.

The results of these studies again confirm our view that both creatin and creatinin may have an exogenous origin from the amino acids of the diet.

Amino-acid therapy had little effect upon the distribution of nitrogen in the urine of 3 cases in the form of the total, urea, ammonia, uric acid and undetermined nitrogen. The increase in creatin and creatinin excretion was affected in only 1 of these cases.

Evidence is presented that the lower motor neurone (tropic unit) with the muscle it innervates must be functionally intact for creatin formation from the amino acids.

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ARTERIOLAR ESSENTIAL HYPERTENSION AND ACTIVE TUBERCULOSIS: THEIR RARE ASSOCIATION.

BY DAVID AYMAN, M.D.,
BOSTON, MASS.

(From the Medical Clinic of the Peter Bent Brigham Hospital.)

It has often been noted that active tuberculosis and arteriolar essential hypertension are rarely found together.¹⁻⁵ Of the more recent and accurate studies of blood pressure in tuberculosis, Grant,⁶ in 1921, found that 5 of 140 patients with pulmonary tuberculosis had a systolic blood pressure above 150 mm. Betchov and Farbargue-Vail⁷ noted that only 1 of 157 tuberculous patients had a systolic blood pressure above 150 mm. Stivelman⁸ found that 10% of 464 tuberculous patients, from 16 to 30 years of age, had blood pressures over 135 mm. and over 140 mm. in older patients. He did not present the actual readings, and it is possible that most of these elevations were between 135 and 150 mm. Masten^{4,9} strengthens this possibility by finding that of 230 tuberculous patients, 6.5% had blood pressures above the average normal; yet, only 2.6% had systolic pressures 150 mm. or more. In 504 cases of active tuberculosis, Bunta^{4,5} found only 1 case with "absolute hypertension," 146 systolic, 88 diastolic. Of 240 cases of active tuberculosis seen by the author, not 1 patient with a blood pressure above 150 mm. was encountered.

The reasons for the rare association of the two diseases are not conclusive. Although essential hypertension is chiefly a disease of midlife, and active tuberculosis primarily a disease of the first three decades, there are many middle-aged persons with active tuberculosis. Of 212 tuberculous patients, the author found that 39% were over 40 and 13% were over 50 years of age; yet hypertension was not encountered. It is possible that the tuberculous toxemia has a hypotensive action and lowers a previously high blood pressure. It is also to be noted that the two diseases tend to occur in different physical types, the hypertensive patient tending to have a short thick neck and a short wide thorax, whereas active tuberculosis tends to occur in the long lean person. It is possible that the former type is more capable of resisting tuberculosis.⁴ Finally, it is stated that on the uncommon occasions when arteriolar hypertension and active tuberculosis occur together, the tuberculosis is apt to be mild, of the fibroid type and but slightly progressive.^{1,2,3,6,7}

It is clear that the two diseases occur together rarely, and when they do, the tuberculosis tends to be mild. It is important to know (1) whether hypertensive patients really have had tuberculous infection in early life as often as non-hypertensive people, and (2) what is the nature of the apparently greater resistance of the hypertensive patient to active tuberculosis.

Present Study. Since it is known that from 80% to 100% of adults have positive skin reactions to tuberculin¹⁰ and have post-mortem findings of healed tuberculosis,¹¹ it would seem likely that most if not all hypertensive patients would also have such evidence of old tuberculous infection. Yet it is possible that a much lower incidence of positive tuberculin reactions and of healed tuberculosis at postmortem might be found in hypertensive patients. This possibility has been checked by (1) analyzing for tuberculosis the family history, past history and postmortem findings in a group of hypertensive patients, and (2) carrying out the routine intracutaneous tuberculin test in a group of hypertensive patients.

To determine whether the hypertensive patient has a different degree of resistance or immunity to tuberculosis, the tuberculin test has been utilized further. The relationship of the intracutaneous tuberculin reaction to immunity and resistance is not settled. Many believe that the tuberculin reaction and immunity tend to parallel each other.¹² Yet it has recently been reported that a high degree of reaction to tuberculoprotein seems to hasten the progress of tuberculosis rather than increase resistance.¹³ Which-ever of these conflicting ideas is correct, it would be of value to know whether hypertensive patients react to tuberculin in a greater or lesser degree than non-hypertensive persons. Therefore, in the present study, instead of using only the usual 1 to 1000 dilution

of tuberculin, dilutions up to 1 to 100,000 were used in order to note any difference in reaction between hypertensive and non-hypertensive persons.

The patients used in this study were: (1) Hypertensive ward patients with blood pressure readings of 160 systolic, 90 diastolic or more; and (2) ward patients beyond the age of 45, in whom the blood pressure was systolic 130 or less and diastolic less than 90 mm.

Results. 1. *Family and Past Histories of Tuberculosis in Hypertensive Patients.* Analysis of the records of 190 ward patients with essential hypertension and of 101 ward patients with normal blood pressure, and beyond the age of 45, showed a similar incidence of pleurisy, past and family histories for tuberculosis (Table 1).

TABLE 1.—INCIDENCE OF TUBERCULOUS HISTORIES IN (1) HYPERTENSIVE PERSONS, AND (2) PERSONS WITH NORMAL BLOOD PRESSURE.

	Family history of tuberculosis. %	Past history of tuberculosis. %	Past history of pleurisy. %
190 hypertensives	16	1.6	3.2
101 controls	21	3.0	0

2. *Postmortem Evidence of Tuberculosis in Essential Hypertension.* The postmortem records of 80 patients with essential hypertension were analyzed for evidence of tuberculosis. Of the 80 patients, 56 died of heart failure or cerebral hemorrhage; 10 of the 80 died of lobar or bronchopneumonia; the remaining 14 of cancer, cirrhosis of liver, etc. In 46 of the 80 cases, the pleura had old fibrous adhesions over the upper lobe, usually at the apices, and often in both lungs. Cases with fresh adhesions or adhesions at the bases only were not included in the above 46 cases. In 14 of the 80 cases there was a family history of tuberculosis, and in 10 of the 14, adhesions were present but in no more abundance than in those with no family history of tuberculosis. In 19 of the 80 cases there were grossly calcified areas seen in the lung parenchyma. In 6 other cases, microscopic evidence of tuberculosis of the hilar or mesenteric glands was found. In 1 of these cases, caseous necrosis was seen, while from another case an injection of gland material into a guinea pig gave positive results for active tuberculosis. In the latter case there was no clinical evidence of active tuberculosis.

3. *Reactions of Hypertensive Patients to Different Dilutions of Old Tuberculin.* A group of 40 ward hypertensive patients, average age of 58, and 55 ward patients with normal blood pressure, average age of 50, were studied with varying dilutions of intracutaneous tuberculin injections. The dilutions and amount used were 0.1 cc. of 1 to 1000, 1 to 10,000, 1 to 50,000 and 1 to 100,000. Each patient received the 4 injections at one time at separate sites on the forearms. At the end of 48 hours the reactions were read in

millimeters in three dimensions. Any area of induration was considered a positive reaction.

As seen in Table 2, there was a similar percentage both of positive reactions and of size of reactions to the varying dilutions, in the hypertensive persons as compared with the patients with normal blood pressure. In general, there was no significant difference in the amount of elevation of induration in either group of patients.

TABLE 2.—POSITIVE REACTIONS TO TUBERCULIN IN HYPERTENSIVE PERSONS AND THOSE WITH NORMAL BLOOD PRESSURE.

Dilution of tuberculin	1 to 1000	1 to 10,000	1 to 50,000	1 to 100,000
Positive reactions, %:				
40 hypertensives	90.0	55.0	42.0	30.0
55 controls	91.0	61.0	33.0	26.0
Average diameter of reactions, mm.:				
40 hypertensives	19.0	10.9	5.7	6.0
55 controls	16.6	8.0	5.2	5.7

Summary and Conclusions. Analyses of postmortem findings, and of the past and family histories showed that the hypertensive patients had tuberculous infection at some time in life. Studies with tuberculin showed that 90% of the hypertensive patients and 91 per cent of the controls with normal blood pressure had tuberculous infection at some time in the past. The analyses of the reactions to the 1 to 10,000, 1 to 50,000 and 1 to 100,000 dilutions of tuberculin, used in an effort to disclose different degrees of sensitiveness or resistance, showed no significant difference in frequency or size of reaction in the hypertensive patients as compared with the control subjects. Therefore, while clinical experience indicates that arteriolar essential hypertension and active tuberculosis occur together uncommonly, the present study does not supply the reason for this observation.

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DELAYED RESOLUTION IN LOBAR PNEUMONIA AND ITS RELATIONSHIP TO PREEXISTING SYPHILIS.

BY ALBERT WEINSTEIN, M.D.,
RESIDENT PHYSICIAN, VANDERBILT UNIVERSITY HOSPITAL,
NASHVILLE, TENN..

AND

MORTON GOODMAN, M.D.,
ELI LILLY RESEARCH FELLOW IN MEDICINE,
BALTIMORE, MD.

(From the Syphilis Division of the Medical Clinic, The Johns Hopkins Hospital, and the Department of Medicine, Vanderbilt University Medical School.)

THE conception that syphilis predisposes to the complications of acute lobar pneumonia and particularly to delayed resolution has been advanced by Fitz-Hugh,¹ Kampmeier², and Youmans and Kampmeier.³ Others, for example Lieven,⁴ are not in accord with this view. In the reports of each of the above-mentioned authors the number of patients studied is relatively small. It seemed desirable to evaluate the possibility that syphilis may be a factor in predisposing to delay of resolution in lobar pneumonia, and an analysis of 509 cases is reported in this communication. The recent occurrence on the wards of the Johns Hopkins Hospital within a period of 2 months of 3 cases of unresolved pneumonia in patients with syphilis gave an added impetus to this study.

Material. The material for this analysis includes: (1) All cases of acute lobar pneumonia admitted to the Johns Hopkins Hospital for the 8-year period ending, May, 1933; (2) all the cases of acute lobar pneumonia admitted to the Vanderbilt University Hospital for the same period; (3) all patients with this infection admitted to the Baltimore City Hospital for the years 1929-1932, inclusive; (4) certain observations also were made on all the cases in the files of the Pathological Department of the Johns Hopkins Hospital with a necropsy diagnosis of chronic fibroid pneumonia, bronchiectasis, lung abscess, organizing pneumonia or unresolved pneumonia for the 7-year period ending, May, 1931.

We selected 509 cases of acute lobar pneumonia from almost 900 protocols, including only those records in which the Wassermann reaction on the blood serum had been recorded, in which there was no antecedent pulmonary disease, such as tuberculosis, and in which there was no question whatever of the diagnosis of lobar pneumonia. The clinical symptoms and signs were essentially characteristic in each instance. Demonstration of the etiologic pneumococcus was obtained in the majority of the cases. Patients treated with Type I antipneumococcus serum are excluded.

Analysis of Cases of Lobar Pneumonia. The patients are almost equally distributed in number between the white and colored races—white, 262 (51.5%); colored, 247 (48.5%). Of the entire group, 139 (27.3%) had syphilis; 50.2% of the colored group were syphilitic as compared with 6.9% of the white patients. The 4 main groups

of pneumococcus appear with equal frequency in the syphilitic and non-syphilitic cases.

The cases are arbitrarily placed for study into 4 main clinical groups according to the clinical outcome: (1) Crisis; (2) lysis in 7 days or less; (3) lysis in 7 to 14 days; (4) lysis in 15 or more days.

Crisis. In this group are placed those patients in whom the acute phase of the disease terminated by fairly abrupt clinical improvement characterized by a sharp fall in the temperature, pulse and respiratory rate, and followed shortly by a disappearance of abnormal physical signs. Termination of the pneumonia by crisis occurred in 141 (27.7%) of the 509 patients. This phenomenon occurred in 39 (28%) of the group with syphilis and in 103 (27.5%) of the non-syphilitics. In patients with syphilis, crisis occurred in an average of 7.2 days, and in the non-syphilitic group, in 7 days.

TABLE 1.—CLINICAL OUTCOME OF PNEUMONIA IN SYPHILITIC AND NON-SYPHILITIC CASES.

	Clinical outcome.	
	Total syphilitic, 139 cases.	Total non-syphilitic, 370 cases.
Crisis	39 (28.0%)	102 (27.5%)
Lysis in less than 7 days	26 (17.0%)	88 (23.7%)
Lysis in 7 to 14 days	9 (6.4%)	34 (9.1%)
Lysis in more than 15 days "unresolved pneumonia"	15 (10.7%)	30 (8.1%)
Empyema	5 (3.6%)	23 (6.2%)
Died:		
Pneumonia or direct complications	31 (22.3%)	74 (20.0%)
Pneumonia complicated by other diseases	14 (10.0%)	19 (5.1%)

Lysis in less than 7 days: In this group are included those patients in whom the pneumonia underwent a less abrupt clinical improvement. The physical signs cleared and the temperature and pulse fell gradually to normal over a period of 7 days or less. Such resolution occurred in 26 (17%) of the syphilitics and in 88 (23.7%) of those without syphilis.

Lysis in 7 to 14 days: This classification includes those patients in whom termination of the disease was associated with a gradual defervescence of fever and pulse rate and the clearing of abnormal clinical and roentgenologic signs over a period of 2 weeks from the beginning of recovery. This type of healing occurred in 9 (6.4%) of the group with syphilis and in 34 (9.1%) of those without this infection.

Lysis in 15 days or more: In this group are included those patients who, though much improved or essentially clinically well, continued to exhibit abnormal physical signs or substantial changes in the Roentgen ray films of the chest for more than 2 weeks after the termination of the acute phase of the illness. Such a classification is designed to include those cases ordinarily diagnosed as "delayed resolution" or "unresolved pneumonia." Of the 45

patients in this group, 15 had syphilis and 30 had not. Of the 139 cases in the entire series with syphilis, 10.7% showed such a retarded resolution as compared with 8.1% of the 370 patients who were non-syphilitic. The age distribution of the patients in this class paralleled roughly that of the whole group. No particular lobe of the lung seemed to be involved with undue frequency. The occurrence of the various types of pneumococci in these cases corresponded quite closely with their frequency in the entire series, except for the pneumococcus Group III which occurred but once.

Other Complications of Pneumonia. Bacteremia was noted with about equal frequency among the syphilitics and the non-syphilitics with pneumonia. Empyema occurred in 28 of the 509 cases. This complication was present in 23 (6.2%) of the non-syphilitic group in contrast to 5 instances of it (3.6%) in the group with syphilis. It is of interest that empyema occurred 3.5 times as frequently in the white race as in the colored (22 in 262 white patients; 6 in 247 colored patients). Of the 4 cases which developed lung abscesses, 2 were syphilitic and 2 non-syphilitic. Bronchiectasis was not noted as a sequel of pneumonia, though in many instances the patients were not followed for a period sufficiently long to note the development of such late complications.

Mortality. Of the 509 patients reviewed in this series, 138 (27.1%) died. Of these, 105 died directly of pneumonia or complications of this infection (pneumococcus endocarditis, pericarditis, empyema, etc.), while the other 33 patients exhibited associated illnesses which contributed to death (heart disease, diabetes mellitus, etc.). Of the 105 patients who died of pneumonia or its direct complications, there was proportionate distribution among the syphilitics—31 cases (22.3%)—and the non-syphilitics—74 (20%).

Necropsy Data. An attempt was made to determine whether any relationship existed between syphilis and chronic pulmonary infection other than that directly attributable to an antecedent attack of acute lobar pneumonia. For this purpose the autopsy records of the Johns Hopkins Hospital were reviewed for the 7-year period ending, May, 1931. The lesions included in this survey were those indexed as chronic fibroid pneumonia, lung abscess, empyema, bronchiectasis and organizing pneumonia. The following groups of cases were excluded: (1) Infants and children under 15 years of age and all those above this age with congenital syphilis, since this study is concerned only with acquired syphilis; (2) all patients in whom some obvious extrathoracic focus was the source of metastatic pulmonary infection; (3) tumors of the mediastinum producing bronchial obstruction with resultant bronchiectasis, a group which included several cases of aneurysm of the aorta; (4) pulmonary infection associated with neoplasm; (5) those cases in which the blood Wassermann reactions were not recorded in the clinical records; (6) all granulomatous infections of the lungs (tuberculosis,

fungus, infection, etc.); (7) all instances in which pulmonary infection was obviously fairly acute in its histologic appearance or less than 3 or 4 weeks' duration as judged from the clinical history. In short, the cases selected for study are those of chronic pulmonary infection of one form or another, other than those residual lesions directly traceable to lobar pneumonia.

During this 7-year period, 4000 necropsies were performed in the Johns Hopkins Hospital. After the groups indicated above are excluded, only 30 protocols of cases with chronic pulmonary infection remain for analysis. Of these, only 5 (16.6%) were syphilitic, a figure which is quite close to the general hospital incidence for this infection.⁵ It appears from these data that there is no appreciable predisposing relationship between syphilis and chronic pulmonary infection as defined above.

Results of Antisyphilitic Treatment in Unresolved Pneumonia. Head and Seabloom,⁶ in 1919, reported beneficial results following the administration of arsphenamin to 3 colored male syphilitic patients with unresolved pneumonia. The injections of the drug were started 4, 6 and 9 weeks, respectively, after the temperature became normal. These writers were of the opinion that the specific treatment hastened the process of resolution in these cases.

Four of the patients in this report, in whom resolution of pneumonia was delayed for over a month ("unresolved pneumonia"), received antisyphilitic treatment.

Case Abstracts. CASE 1.—A. T. (Unit No. 49201) contracted syphilis 2 years before the onset of pneumonia. He was given 8 injections of arsphenamin and 16 of a bismuth preparation over a period of 9 months, the last treatment being administered 9 weeks prior to the onset of his acute illness. He was admitted to the wards on the 4th day of pneumonia, with consolidation of all lobes of his lungs except the left upper. Group IV pneumococci were isolated from the sputum. The temperature began to drop on the 6th day of his illness, and, though it was quite normal 5 days later, resolution of the pulmonary consolidation was very much delayed. On the 31st day after the temperature had become normal he still showed extensive signs of unresolved pneumonia, though the process was slowly clearing. Potassium iodid, 6 gm. daily, was started at this time; and on the 40th afebrile day he received 0.3 gm. of neoarsphenamin intravenously. He then received arsphenamin, 0.4 gm., intravenously, once a week for 4 weeks. At the end of this time he still presented definite roentgenographic and physical signs of unresolved pneumonia at both bases. He was then given at weekly intervals 4 injections of bismuth salicylate, 0.2 gm., and then arsphenamin again for 3 weeks. At the end of this time a Roentgen ray film of the chest showed that the lungs were essentially clear but there was still demonstrable some percussion impairment and a few râles at both bases. Each of several observers felt that there was no conspicuous acceleration of absorption of the unresolved pneumonic process in this case after the institution of antisyphilitic treatment.

CASE 2.—R. A. (Unit No. 48665), a colored male, aged 45, was admitted on the 8th day of lobar pneumonia. He was very ill and showed physical signs indicating consolidation of his entire right lung. The temperature fell gradually to normal within a week and, although he felt quite well,

physical and roentgenographic signs had cleared but little. After the temperature had remained normal for 1 week he was given 3 gm. of potassium iodid a day and 0.2 gm. of bismuth salicylate intramuscularly every 5 days. This therapy was continued for 4 weeks, during which time slight resolution of the lung lesion was noted. He was then given 0.1 gm. neoarsphenamin intravenously (he had syphilitic aortitis and the initial treatment was accordingly mild), and was discharged to the Out-patient Department. He did not return, however, until 3 weeks later and at that time, though the Roentgen ray examination showed almost complete clearing, minimal signs of consolidation were still demonstrable.

A third patient is described here in considering the effect of antisyphilitic treatment, though he is not considered above in the analysis of clinical cases because he received antipneumococcus serum.

CASE 3.—J. P. (Unit No. 49363), a colored male, aged 24, developed a penile chancre for which he received 5 injections of arsphenamin. He failed to return to the clinic for further treatment for 2 months, after which time he returned with a neurorecurrence. He was then given 2 injections of 0.5 gm. arsphenamin at weekly intervals. Two days after the last injection he became acutely ill with lobar pneumonia. The illness was unusually severe. Group I pneumococci were cultured from his blood. He was treated with Felton's antipneumococcus serum. Abnormal physical signs and changes in the Roentgen ray persisted for some time after clinical improvement began and were still quite prominent 21 days after the beginning of resolution. He received 0.3 gm. of neoarsphenamin, and this dose was repeated 2 weeks later. Arsphenamin, 0.4 gm., was then given at weekly intervals. Throughout this period there was continued slow resolution of the lung lesion, and it was not until $1\frac{1}{2}$ months after the temperature became normal that the lungs were considered clear. None of several observers felt that treatment for syphilis had materially hastened the absorption of the pneumonic lesion.

CASE 4.—G. S. (Unit No. 41479), a colored female had been receiving antisyphilitic treatment steadily for 7 months prior to her admission to the hospital with pneumonia. She was admitted on the 3d and died on the 33d day of her illness. She was always acutely ill and the signs in the lungs changed but little during the period of observation. At necropsy she was found to have organizing pneumonia with extensive scarring of both lungs. She received no antisyphilitic treatment after she became acutely ill.

Discussion. Youmans and Kampmeier³ reported that among 30 cases with postpneumonic complications, 12 (40%) were associated with preëxisting syphilis. In our series of 509 cases the clinical course of lobar pneumonia was not perceptibly different in patients with and without syphilis. A classical "crisis" occurred with the same frequency on the two groups. The incidence of delay of resolution beyond 15 days from the time of the beginning of recovery was not significantly greater in the syphilitic (10.7%) than the non-syphilitic (8.1%) patients. The mortality rates of those patients who died directly of the pneumococcus infection was essentially the same in those with and those without preëxisting syphilis. Of the patients in whom factors other than pneumonia contributed to death, it is quite to be expected that the death rate should be higher in those with syphilis for several patients who were

already quite ill with cardiovascular syphilis are here included. It was noted that empyema as a complication of lobar pneumonia is $3\frac{1}{2}$ times as common among the whites as the colored. The total number is perhaps too small to warrant undue emphasis on this fact.

In 30 carefully selected necropsy-proved instances of chronic pulmonary infection, the incidence of evidence of syphilis is not appreciably higher than the frequency of this disease in the adult hospital population of the Johns Hopkins Hospital. It would appear that there is no undue association of chronic fibroid pneumonia, bronchiectasis, lung abscess or organizing pneumonia and the presence of antecedent infection with syphilis.

In 3 cases recorded there is little to indicate that treatment for syphilis accelerated appreciably the course of resolution of unresolved pneumonia. In a 4th case, resolution was delayed for a month until death in spite of vigorous and continuous treatment for syphilis, up to the time of the onset of pneumonia. It is true that in only 1 of the cases did the patient receive the large amounts of arsphenamin advised by Head and Seabloom,⁶ but the administration of full therapeutic doses of this drug to patients with severe infections associated with anoxemia and the attendant liver damage seems to us not without risk. Though the so-called "nonspecific effect" of the arsphenamin, as a result of which non-syphilitic infectious processes undergo healing, was not noted in our cases, it is conceivable that large doses of the drug may facilitate the absorption of a chronic inflammatory process without any relation to its effect on syphilis.

Summary. 1. The records of 509 patients with acute lobar pneumonia are reviewed. Of these patients, 37.5% had syphilis. The clinical course of the pneumonia was not appreciably different in the syphilitic and non-syphilitic groups.

2. Following acute lobar pneumonia, delay of the process of resolution occurs about as frequently in the syphilitics as the non-syphilitics.

3. The records of 30 patients with necropsy diagnosis of chronic fibroid pneumonia, lung abscess empyema, bronchiectasis and organizing pneumonia, do not show any undue frequency of syphilis.

4. The reported favorable influence of antisyphilitic therapy on the course of unresolved pneumonia was not observed.

We express our thanks to Dr. Thomas R. Boggs for his kindness in placing the records of the Baltimore City Hospitals at our disposal, and to Dr. Joseph Earle Moore, Physician in Charge of the Syphilis Division, for his suggestions and advice.

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BOOK REVIEWS AND NOTICES.

DIE WERKE DES HIPPOKRATES. Herausgegeben von DR. MED. RICHARD KAPFERER unter Mitwirkung von PROF. DR. GEORG STICKER, Würzburg. Part 1. Sitten- und Standleshre für Aerzte (Price, Rm. 2.80); Part 2. Die Altgewährte Kunst/Die Kunst (Price, Rm. 3); Part 5. Die Winde/Die Heilige Krankheit (Price, Rm. 1.50); Part 14. Die Hippokratischen Lehrsätze (Price, Rm. 2.10). Pp.: Parts 1 and 2, 59 each; Part 5, 65; Part 14, 80. Stuttgart: Hippokrates-Verlag G.M.B.H., 1934. (To be published in 25 parts costing ca. Rm. 100, card binding.)

HIPPOCRATES—or better the *Corpus Hippocraticum*—above all classical physicians has unquestionably held the highest position in the estimates of modern medical thought. This was not true, however, for the many centuries in which Galen, Celsus and Avicenna dominated medicine. With the advent of printing, for instance, Hippocrates' collected works were not printed until 1525; the others mentioned had numerous incunabula editions. By the 19th century, however, the position of the Father of Medicine was unassailably established. Between 1839 and 1861, Littré brought out his monumental "*Oeuvres*" in 20 volumes, which successfully utilized the available information to delineate a picture of Hippocratic medicine that still maintains. More useful to English readers is Jones' 4-volume edition in the Loeb Classical Library, with both Greek and English text, both of which we believe are accurate; yet for the scholar, adequate references to check this accuracy are lacking. Complete German editions have not hitherto been outstanding. Incomplete editions by Heiberg and by Ilberg and Kühlemann only partly remedied the situation, so that the announcement of this new German edition was received with lively anticipation. Sigerist has recently surveyed the situation in his customary illuminating manner (*Bull. Inst. Hist. Med.*, Johns Hopkins Univ., 2, 190, 1934). Neohippocratism makes a new venture appropriately timely, yet one wishes that in the pamphlets thus far received there were more garnishings for the main dish. In these parts, preliminary remarks and footnotes are scantier than in Jones, and it becomes obvious that the work is more for the Neohippocratic reader than the scholar.

The present edition will present 75 books in 25 parts, the German text being based chiefly on the *Corpus Medicorum Graecorum*. The Greek text is not included. Of this collection, 4 parts have been received: 1. The Oath, the Law, Honorable Behavior, Precepts, the Physician; 2. Ancient Medicine and the Arts; 5. The Internal Airs or Breaths—The Sacred Disease (Epilepsy); 14. The Aphorisms. In the first of these are 5 propeudetic essays on the physician and his relation to the patient and to other doctors that will always have a practical as well as a historical value. The 2 essays of the second installment are noteworthy, one for the characteristic Hippocratic emphasis on observation rather than theory, the other because it is one recognized through the whole Christian era as most probably written by Hippocrates himself. The 2 works of Part 5 are The Internal Airs (or Breaths, in Jones' translation) and The Sacred Disease—Epilepsy. The Introduction explains that the former of these includes the concepts of inspired miasmatic air, intestinal gases and blood gases (oxygen, carbon dioxide), though the text hardly supports such a modern concept. This matter can be pursued in Axel Nelson's Upsala Dissertation (1909). The tract on Epilepsy is justly renowned, among other reasons, for its attribu-

tion of the disease to the central nervous system rather than to divine agencies. The ascription of the brain disorder and the convulsions to asphyxia also has an altogether modern ring.

The Aphorisms (Part 14), justly praised by the Editor for their divine-like quality, are preceded by an illuminating 12-page Introduction by Sticker. He points to the continued recognition of its great value from Erotian and Galen to Littré and Daremberg. Comprehension of Sticker's analysis of the Hippocratic theory of existence in health and disease, including such concepts as the life force (*physis*), its physiology and pathology, the physician's rôle in diagnosis, prognosis and therapy, will greatly aid in the understanding of any of the Hippocratic writings. We look forward with interest to the appearance of subsequent fasciculi.

E. K.

CLINICAL ASPECTS OF THE ELECTROCARDIOGRAM. By HAROLD E. B. PARDEE, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital; Consulting Cardiologist, Lying-in Hospital and Woman's Hospital, New York City. Pp. 295; 74 illustrations. Third edition, revised. New York: Paul B. Hoeber, Inc., 1933. Price, \$5.50.

ALTHOUGH many have been asserting for some years now that the electrocardiogram has made most of its contributions to medicine, nevertheless the developments in the five years that have elapsed since the appearance of the second edition, have necessitated rewriting most of the chapters. The items chiefly requiring change were the *S-T* interval, the duration of the ventricular complex, large *Q* waves, the *T* wave and the changes resulting from myocardial disease. The author accepts the newer concepts of bundle-branch block and ventricular extrasystoles. The chapter on the theory of the electrocardiogram is especially to be recommended.

E. K.

FRONTIERS OF MEDICINE (A Century of Progress Series). By MORRIS FISHBEIN, M.D. Pp. 207. Baltimore: The Williams & Wilkins Company, 1933. Price, \$1.00.

THIS outline of medical progress since earliest times succeeds in presenting a readable story in its very narrow limits. In the earlier periods the author has wisely enlivened the narrative with quotations and has felt free to deal with topics according to his inclination or to his previous writings rather than based on the general importance of the subject. Thus the entertaining account of Paracelsus' life occupies 19 pages while Vesalius and Harvey are disposed of in a chapter of 4; Internal Medicine occupies 51 pages and Surgery 4; Pharmacology alone among the preclinical subjects has a chapter to itself. The Century of Progress, of which series the booklet is a unit, includes a good account of Beaumont and a paragraph on Chicago developments. The message of the Century of Progress Exposition is conveyed on the back of the jacket. The few hours required for reading this sketch will be well repaid.

E. K.

LETTSON. HIS LIFE, TIMES, FRIENDS AND DESCENDANTS. By JAMES JOHNSTON ABRAHAM. Pp. 498; illustrated. London: William Heinemann, Ltd., 1933. Price, 30/ net.

ONE does not have to read the author's preface to realize that this biography of the great Quaker physician is a labor of love; the fact is evident in every page of this sumptuous volume. And a colorful life it

was to be depicted. From Lettsom's birth in the dwindling Quaker colony at Tortola in the West Indies, through his schooling in England, apprenticeship to the apothecary-surgeon, Sutcliff, of Settle, Yorkshire, "walking the wards" at St. Thomas', six months with Cullen, and an M.D. degree at Leyden, to his highly successful and philanthropic career in London, all is spread out for us with sufficient attention to detail and background to get a vivid picture both of the man and his times. As founder of the General Dispensary, Lettsom started a new era in the treatment of London's poor. A lifelong supporter of the Royal Humane Society, his quite modern publicity sense appears in the procession that he arranged around the room after the annual dinner of those "who had been raised from the dead." Lettsom's activities in much needed prison reform would alone be sufficient to preserve his fame, while the foundation of the Royal Sea Bathing Hospital—his most important medical contribution—is regarded as "the father of all the open-air sanatoria throughout the world" (p. 276). Founder of the famous Medical Society of London, he is perhaps best known to physicians through the frequently reprinted engraving of Lettsom presenting the deeds of No. 3 Bolt Court to the Medical Society. Perhaps even better known is the verse which, according to our author, has kept Lettsom's memory green. In the original of its more than 20 variants it reads:

"You say I'm dead, I say you lie,
I physics, bleeds and sweats 'em
If after that my patients die,
Why verily—J. Lets 'em."

E. K.

COLLENS SYSTEM OF DIET WRITING, Including Diet Calculator, Obesity Chart, 100 Menu Prescription Forms. By WILLIAM S. COLLENS, B.S., M.D., Chief, Diabetic Clinic, Israel Zion Hospital; Assistant Physician, Greenpoint Hospital; Metabolist, Brooklyn Women's Hospital; Consulting Metabolist, Rockaway Beach Hospital. New York: Form Publishing Company, 1933. Price, \$5.00.

A DEVICE for calculating and prescribing quantitated diets for patients with such conditions as diabetes, nephritis, or obesity, that possesses the advantage of being simple, sufficiently accurate, very flexible in its range, convenient for the physician, and easily intelligible for the patient: quite the most practical device of the kind known to the Reviewer.

R. K.

THE 1933 YEAR BOOK OF RADIOLOGY. DIAGNOSIS. Edited by CHARLES A. WATERS, M.D., Associate in Roentgenology, Johns Hopkins University; Assistant Visiting Roentgenologist, Johns Hopkins Hospital. **THERAPEUTICS.** Edited by IRA I. KAPLAN, B.Sc., M.D., Director, Division of Cancer, Department of Hospitals, City of New York; Clinical Professor of Surgery, New York University and Bellevue Medical College. Pp. 804; 780 illustrations. Chicago, Ill.: The Year Book Publishers, Inc., 1933.

THE same general plan, so successfully employed in the first of the series of Year Books, has again been utilized in this present volume. The book presents a résumé of the radiologic literature for the past year and appears to be even more comprehensive than the preceding contribution. This work should have a universal appeal, not alone for the radiologist but for all practitioners of medicine. There is no specialist or general practitioner who will not find much to interest him in this volume. It should serve a very useful purpose in keeping all abreast of the rapid advances being made in radiology.

K. K.

MEDICINE IN PERSIA. By CYRIL ELGOOD, M.D., M.R.C.P., Late Physician to the British Legation, Teheran, Persia. Vol. 14 of *Clio Medica*. Pp. 105; 11 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, \$1.50.

CLIO MEDICA has done wisely in adding a volume on Persian medicine to its valuable list of historical compends. Not many are aware of the fact that a large part of Arabian medicine is in reality Persian. The Arabs in conquering Persia not only displaced Zoroastrianism by Islamism, but they also substituted their language and script for the ancient Aryo-Persian. The great Arabian medical writers of the Middle East, of which Bagdad was for a long time the cultural center, were, as a rule, native Persians, although of diverse religions—Mohammedan, Jewish, Nestorian Christians. All used the Arabian language in their writings, just as French, German, English and Italians wrote in Latin during the Middle Ages.

The author, as physician to the British Legation in Teheran, had excellent opportunities, of which he made wise use, of acquainting himself with the medical history of Persia. He gives a good account of the great medieval epoch that produced men of the stamp of Rhazes, Avicenna, Haly Abbas and others, men whose influence upon the medicine of Western Europe was much greater than earlier historians believed. Avicenna's *Canon* was a textbook in Europe until the close of the seventeenth century. However, after the Tartar conquests, under Jenghiz Khan and Tamerlane, Persian medicine went into an eclipse from which it is just beginning to emerge. At the present time the custom of young Persians to complete their medical education in Beirut or Paris, together with the Pasteur Institute, founded at Teheran in 1921, have made medicine in modern Persia largely French. Persian art which reached so high a degree of perfection in former centuries has left many unusual anatomic drawings, some of which are reproduced in Elgood's book.

D. R.

GERMAN MEDICINE. By W. HABERLING, M.D., Professor of the History of Medicine, Academy of Düsseldorf. Translated by JULES FREUND, M.D., Ex-Associate in Bacteriology, University of Pennsylvania. Vol. 13 of *Clio Medica*. Pp. 160; 9 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, \$1.50.

It is surprising how much of the history of German medicine the author has crowded into this little book. Beginning with primitive times, he carries us rapidly down through the Middle Ages to the modern period. The Middle Ages were far more sterile in German lands than in the Latin countries. For example, the great thirteenth century, so fertile in all directions—in literature, in art, in architecture—in France, in Italy and in Spain, had no counterpart in Germany. The great anatomist Vesalius was not appreciated in Germany until sometime after his death. It is, however, to the credit of German medicine that the doctrines of Harvey were at once espoused with great enthusiasm. The first real awakening came with Paracelsus; but after him, for nearly 200 years, there is no great original figure until Albrecht von Haller, a man of encyclopedic mind.

What Germany lost by its early slowness, by the depressing effects of the Thirty Years War, has been amply made up in the last 100 years. The pupil became the master. But will it remain so? Or will the return of medieval psychology affect the progress of science and medicine unfavorably?

D. R.

INDUSTRIAL TOXICOLOGY. By ALICE HAMILTON, M.D. Pp. 329. New York: Harper & Brothers, 1934. Price, \$3.

THE ever-increasing complexity and multiplicity of chemical processes in industry bring with them industrial hazards and poisonings which are bound to come under the observation of numerous practitioners of medicine. This handy pocket-size volume, written by the leading authority on the subject in this country, should be read by all physicians who practise in an industrial community.

R. K.

DISEASES PECULIAR TO CIVILIZED MAN. By GEORGE CRILE, M.D. Edited by AMY ROWLAND. Pp. 427; 41 illustrations. New York: The Macmillan Company, 1934. Price, \$5.

THE principle of orthogenesis ("straight creation") is explained as the mechanism whereby a species, beginning to vary definitely in a given direction, continues in that direction even if it thereby tends to its own destruction. It is here evoked "to account for the rise of the brain and the nervous system and the thyroid gland." Later the author adds the adrenals (why not also the pituitary, pancreas and gonads?) to his kinetic system, which in man's phylogenic development have become overactive, producing hyperthyroidism, neurocirculatory asthenia, peptic ulcer, diabetes (sometimes qualified as "probably")—"diseases peculiar to civilized man." Epilepsy, psychoneurosis and hypertension are also considered. The author recommends that this "hyperkineticism" be lessened by sympathectomy, thyroidectomy, adrenal denervation or rationalization. (N.B.—This term has not been defined here but is obviously not used in the customary sense of substituting plausibly rational motives for the protective reactions of the psychoneurotic.) His success with adrenal denervation in some 230 cases leads him to believe that the individual may be saved even though the species may be going on to destruction "by the same tool that enabled him to reach the greatest height of his civilization." More than half of the book is taken up with case histories, which also supply most of the evidence—of the sort that case histories are apt to supply. A proof of the truth of the principle of orthogenesis is fortunately not attempted.

E. K.

WHO SHALL SURVIVE? A New Approach to the Problem of Human Interrelations. By J. L. MORENO, M.D. Pp. 437; illustrated. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1934. Price, \$4.

STUDIES were made from a public school, a state training school for girls and a neighborhood house in New York City. Whereas the psychoanalytic method is subjective, extending backward to past psychic trauma, this approach is through developing the individual's spontaneability with analysis of present performances together with appropriate environmental consideration.

It was observed that when children were free from supervision they arranged themselves roughly into three groups—isolates, pairs and those that adhered to leaders. Further studies were made by interviewing mothers, teachers and housemothers of cottages. The most informative data were obtained through "sociometric tests," wherein individuals choose the 5 girls they liked best, whether from their own cottage or from any other, and with these they then lived. The emotional reactions recorded through descriptions and graphs show attractions, mutual attractions, repulsions, mutual repulsions, indifferences, mutual indifferences and other interesting features.

The hypothesis, "that members of the superior class produce with members of the inferior class better offspring in general than when they remain in their own sphere," offers a ray of hope and it is intimated that, through planning, some of the unfit may propagate and thus modify or discard such palliative measures as sterilization.

Such constructive efforts may enable us to outsmart Nature!

N. Y.

PRACTICAL METHODS IN BIOCHEMISTRY. By FREDERICK C. KOCH, Professor of Physiological Chemistry, University of Chicago. Pp. 282; 17 illustrations. Baltimore: William Wood & Co., 1934. Price, \$2.25.

THE author has drawn upon a large experience in preparing this manual of biochemical methods. Good features of the book include excellent fine-print discussions, a choice of several methods in many instances, and illustrations of the more complicated apparatus.

In the opinion of the Reviewer this manual should prove more suitable for a hospital laboratory than for a teaching course. Some of the methods presented are too long and complicated for general class use. The black type headings are often too informative. The data involved in the preparation of reagents used in the various methods are gathered in an appendix. This type of presentation would have advantages where technicians are employed, but appears inconvenient from the standpoint of proper teaching.

D. D.

THE LABORATORY NOTEBOOK METHOD IN TEACHING PHYSICAL DIAGNOSIS AND CLINICAL HISTORY RECORDING. By LOGAN CLENDENING, M.D., Professor of Clinical Medicine in the University of Kansas. Pp. 71. St. Louis: The C. V. Mosby Company, 1934. Price, 50 cents.

OBVIOUSLY the purpose of this laboratory notebook is to have each student record with care and without omissions his physical findings. While the Reviewer feels that the method of teaching recommended by the author is sound and appropriate, this notebook has no particular advantage over mimeographed sheets containing essentially similar headings. By the use of these headings the student can record his findings on blank paper unhandicapped by the abomination of printed forms and at the same time he is being trained to record his findings in a style which will later be acceptable as permanent hospital record.

S. L.

NEW BOOKS.

A Textbook of Histology. Functional Significance of Cells and Intercellular Substances. By E. V. COWDRY, Professor of Cytology, in the School of Medicine, Washington University, St. Louis. Pp. 503; 242 illustrations. Philadelphia: Lea & Febiger, 1934. Price, \$5.50.

Jöns Jacob Berzelius. Autobiographical Notes Published by The Royal Swedish Academy of Sciences through H. G. SÖDERBAUM. Translated from the Swedish by OLOF LARSELL, Professor of Anatomy, University of Oregon Medical School, Portland. Pp. 194; illustrated. Baltimore: The Williams & Wilkins Company, 1934. Price, \$2.50.

Clinical Toxicology. Modern Methods in the Diagnosis and Treatment of Poisoning. By ERICH LESCHKE, Professor of Internal Medicine in the University of Berlin. Translated by C. P. STEWART, M.Sc., Ph.D., Lecturer in General Biochemistry, University of Edinburgh; Senior Biochemist, Edinburgh Royal Infirmary, and O. DORRER, Ph.D., Research Assistant to Professor Wieland, Munich. Pp. 346; 25 illustrations. Baltimore: William Wood & Co., 1934. Price, \$5.00.

Annals of the Pickett-Thomson Research Laboratory, Vol. 10, Monograph 16, Part 2, Influenza. With Special Reference to the Complications and Sequelæ, Bacteriology of Influenzal Pneumonia, Pathology, Epidemiological Data, Prevention and Treatment. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Honorary Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London, and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 916; illustrated. Baltimore: The Williams & Wilkins Company, 1934. Price, \$17.50.

Bacteriologia. By DR. JOSÉ DE CARVALHO LIMA, Director of Institute of Bacteriology of São Paulo. Pp. 553; many colored illustrations. São Paulo, Impressora Paulista, 1933. (Price not given.)

Human Sterility. Causation, Diagnosis and Treatment. By SAMUEL RAYNOR MEAKER, M.D., Professor of Gynecology, Boston University School of Medicine; Gynecologist, Massachusetts Memorial Hospitals, etc. Pp. 276; 27 illustrations. Baltimore: The Williams & Wilkins Company, 1934. Price, \$4.00.

Marriage Hygiene, Vol. 1, No. 1, August, 1934. First Issue. A Quarterly. Edited by A. P. PILLAY. Pp. 111; 3 illustrations. Bombay: The Times of India Press, 1934. Price, per issue, s. 4/6 or Rs. 2/8; Yearly, s 18/- or Rs. 10/-.

Hygiene for Freshmen. By ALFRED WORCESTER, A.M., M.D., Sc.D., Henry K. Oliver Professor of Hygiene, Harvard University. Pp. 151. Springfield, Ill.: Charles C Thomas, 1934. Price, \$1.50.

NEW EDITIONS.

A Textbook of Pathology. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.C.S., Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg. Pp. 1047; 416 illustrations and 8 colored plates. Second edition thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$10.00.

Internal Medicine. Its Theory and Practice. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane University of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hospital, New Orleans. Pp. 1288; 35 illustrations. Second edition thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$10.00.

Physical Diagnosis. By RICHARD C. CABOT, M.D., Professor of Clinical Medicine Emeritus in Harvard University; Formerly Chief of the West Medical Service at the Massachusetts General Hospital. Pp. 540; 317 illustrations. Eleventh edition. Baltimore: William Wood & Co., 1934. Price, \$5.00.

"The book has been revised and reset throughout. Of special importance is the newly written chapter on the *electrocardiogram*, profusely illustrated by new cuts kindly furnished me by Dr. Paul D. White of the Massachusetts General Hospital. The section on *Subacute Infectious Endocarditis* has been rewritten so as to include the newer data on this important subject. *Coronary Heart Disease*, on which so much new material has come to light since the last edition of this book, is much more adequately described in this edition. The *measurement of cardiac reserve* is discussed. A section on *Pulmonary Heart Disease* has been added, and an account of *The Heart in Myxoedema* containing the newly recognized facts. The section on *Tuberculosis* has been enlarged. . . . *Cancer of the Bronchi and Lung* . . . is in this edition newly described." (From Author's Preface.)

Essentials of Histology. By SIR E. SHARPEY-SCHÄFER, F.R.S., Formerly Professor of Physiology in the University of Edinburgh. Thirteenth edition edited by H. M. CARLETON, M.A., B.Sc., D. PHIL., Lecturer on Histology in the University of Oxford; Research Fellow of New College, Oxford. Pp. 618; 721 illustrations. Philadelphia: Lea & Febiger, 1934. Price, \$5.00.

PROGRESS OF MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF
CARY EGGLESTON, M.D.,
ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND
SOMA WEISS, M.D.,
ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

INDICATIONS AND DANGERS OF THE USE OF BARBITURIC ACID DERIVATIVES.

SOME 30 years ago Fischer and von Mering¹ established the fact that while barbituric acid, a derivative of urea and malonic acid, is physiologically relatively inactive, the substance obtained by replacement of the two hydrogen atoms by ethyl radicals is a powerful hypnotic in animals and in man. Since this discovery a large number of other barbituric acid derivatives have been prepared by replacing one or both atoms by alkyl, cyclic and other radicals. Partly through their beneficial effects in certain conditions and partly through the zeal of the manufacturing houses these substances, introduced under various trade names, have become widely used in different branches of medicine. Veronal, luminal, ipral, amyta, allonal, dial, pernocton, somnifen, nembutal, and evipan are but a few of the trade names of the more commonly used barbituric acid derivatives. The barbituric acid derivatives are certainly among the most widely used drugs today. Not only are they popular as sedatives and hypnotics, but they are also used by some as anesthetics. The literature on the subject is voluminous and cannot be covered in a short review. Most of the contributions are characterized by claims of the low toxicity and relatively high hypnotic and analgesic action of the specific derivative discussed. Usually the popularity of such a preparation, reached mainly through direct and indirect advertising, wanes as a result of the personal experiences of physicians or of a more effective advertisement of a new preparation.

Although the main action of the various barbituric acid derivatives is the same, certain definite advances, particularly with reference to the persistence of action and the elimination of certain undesirable side

actions, have been made in recent years. The *chemistry* and the corresponding trade names of the most frequently used preparations have been discussed recently by Collins and Leech.² Among the numerous studies attempting to compare the chemical structure with the *pharmacologic action*, those of Dox and Hjort^{3,4} are of particular interest. The relative anesthetic value was highest in the ethyl-iso-butyl, the ethyl normal butyl, the ethyl-iso-amyl and the ethyl normal hexyl barbituric acids, as compared with a large number of other members of the series. In the pharmacologic evaluation of the barbituric acids these authors have pointed out a number of other qualities in addition to the index of the minimal effective and minimal fatal doses. In the estimation of the minimal fatal dose, the time element is also of importance. The absolute amount of the minimal lethal dose of the various derivatives varies considerably, without necessarily altering the therapeutic efficacy of the drugs. The implication of this fact is often not appreciated by physicians.

Among the various types of pharmacologic studies the problem of the *excretion* of the barbituric acid derivatives bears directly on the clinical application. The chemical methods used in the identification and quantitative measurements of the barbituric acids are described in a recent article by Koppanyi, Murphy and Krop.⁵ As early as 1910 Bachem⁶ found that as high as 90% of diethyl barbituric acid (veronal) can be detected in the urine following the subcutaneous administration of small doses. Except in a few publications, the high percentage elimination through the kidneys has been confirmed repeatedly. Koppanyi, Murphy and Krop⁵ found that in men, dogs and cats from 42 to 91% of barbital is excreted in the urine, whereas in fowl only 28.4%. Diuretic measures did not increase the rate of excretion or the total excretion of barbital. The concentration of barbital in the blood showed a sharp decline during the first 2 hours and then dropped slowly. The former is due to fixation by the organs; the latter to renal elimination. Bilaterally nephrectomized dogs failed to recover from barbital anesthesia. Estimation of barbital in various organs has indicated that the skeletal muscles and the kidneys contained particularly large amounts of the drug.

Next to the relative toxicity of the drug, its *persistence of action* is of primary consideration from the point of view of the clinic. On the whole, a barbiturate that possesses the least hypnotic and analgesic effect and has the longest persistence of action is the least desirable. Eddy⁷ has found that among the more commonly used members of the series ethyl-iso-propyl barbituric acid is, for this very reason, undesirable. Of the substances with relatively high analgesic and hypnotic effect, but with a short duration of action, cyclo-hexenylmethyl-N-methyl-barbituric acid (evipan) is of special interest. This substance has been described recently by Weese.⁸ Ten minutes after an intravenous narcotic dose the animals begin to awaken, and in from 30 to 60 minutes they have apparently completely recovered. The rapid detoxication of this barbituric acid derivative has been confirmed this year by the pharmacologic studies of Kennedy and Narayana.⁹ Numerous workers have reported on the other pharmacologic effects of the barbituric acid derivatives. Most of the substances tested produce slight or no fall in arterial blood pressure, even in complete anesthesia. Cer-

tain phases of the carbohydrate metabolism are usually disturbed. Slowing of the respiration is induced. The effect on the gastro-intestinal canal is not prominent.

In *clinical use* the barbituric acids are usually administered by mouth, but some preparations can also be given through subcutaneous, intramuscular and intravenous routes. The latter method has become widespread particularly since 1924, when Dujol and Clément¹⁰ advocated the intramuscular and intravenous use of somnifen in obstetrics, and Fredet and Perlis¹¹ used the same drug for the alleviation of pain in surgical operations. On the Continent such a use of the barbituric acids in surgery spread rapidly. In America this procedure was encouraged mainly by Zerfas, McCallum, Shonle, Swanson, Scott and Clowes.¹² who in 1929 reported on the induction of anesthesia in man through the intravenous administration of the iso-amyl-ethyl barbiturate (sodium amytal). The indiscriminate advocacy of the intravenous use of the barbituric acids has led to numerous serious and fatal accidents in this country and abroad. Simultaneously with the initial spread of the intravenous use of the barbituric acids, Weiss¹³ called attention to the potential dangers of such an application. He advocated that the intravenous anesthetic doses should be regarded as potentially dangerous, particularly in surgery, and that their use should be restricted mainly to emergencies such as acute convulsions in eclampsia, epilepsy and cerebral vascular accidents. In severe cases of poisoning due to local anesthetics, in tetanus, and in persistent hiccough, their use was regarded as justified. The Council on Pharmacy and Chemistry of the American Medical Association in a recent report¹⁴ reiterated its earlier warning against the indiscriminate intravenous use of the barbituric acids.

The most useful and widespread application of the barbiturates is in the field of sedatives and hypnotics. Notwithstanding the extensive literature on the subject, it is still impossible to formulate definite conclusions as to the relative merits of the various members in this respect. The use of the barbiturates has also been advocated in surgery, obstetrics and psychiatry, as well as in the treatment of convulsions of varying etiology, of tetanus, and of strychnin and local anesthetic poisonings.

For *surgical anesthesia*, they have not proved to be efficient. The reason for this is that the pharmacologic properties of all the members of the series indicate that the analgesic effect is not so great as that of some of the volatile anesthetics. The anesthetic dose is a relatively high percentage (50 to 70%) of the fatal dose. Weiss,¹³ from observations on animals and on patients who took barbituric acids with suicidal intent, claims that man is more sensitive to the toxic effects than are animals, and that 23 to 37% of the fatal dose is required to induce sleep, moderate muscular relaxation and partial anesthesia. He has pointed out that pain, sympathetic excitement, worry and fever act antagonistically to the effect of the barbituric acids; where as cerebral depression is synergistic and therefore makes the patients susceptible to the depressant effect. Such an acute depression in the course of a severe operation with possible complications represents a potential danger if non-volatile anesthetics with long persistence of action, such as the barbituric acids, are used. Another danger in the long persistence

of action of the barbituric acids is from postoperative complications, particularly pneumonia. Today the barbituric acid derivatives are used mainly as preoperative and basal anesthetics, orally administered, and as such they are apparently of distinct value. Recently Bogan¹⁵ has reported a study on the comparative adaptability of pernocton, avertin and pentobarbital sodium for basal anesthetics, and concludes that moderate doses of the basal drug are best. He prefers pentobarbital to pernocton. Bogan rightly emphasizes the increased need for postoperative care of the patient if non-volatile basal anesthetics are used. Axelrod¹⁶ reports on the use of allyl-iso-propyl barbituric acid (allurate) as a premedication agent.

We have previously referred to the clinical advantages of cyclohexenylmethyl-N-methyl-barbituric acid (evipan) because of the short duration of its action. Since 1933, when Holtermann¹⁷ first reported his clinical experiences with its intravenous use in gynecology and obstetrics, numerous reports have emphasized this property. Its use is therefore advocated in short surgical procedures. Buerkle-de la Camp¹⁸ has used this anesthetic both as a basal and as a sole anesthetic in some 500 cases. Following the intravenous administration of from 4 to 7 cc. of the drug the patient falls to sleep without preceding restlessness. For anesthesia 9 cc. or more is usually required. Young patients have tolerated as high a dose as 22 cc. Most patients awake from 10 to 30 minutes after the administration of an anesthetic dose. In case restlessness is present or the operation is prolonged, $\frac{1}{2}$ to 1 cc. is reinjected every 5 to 10 or 15 minutes. Although these favorable claims were made only a year ago, certain warnings have appeared already. Jarman and Abel,¹⁹ on the basis of experience in 100 cases, consider evipan a useful addition to surgical armamentarium, but claim that its use is contraindicated in feeble and toxic cases, and in the presence of liver disease. It should be administered only by expert anesthesiologists. In case respiratory embarrassment occurs, carbon dioxide and oxygen mixtures should be administered. Landau and Wooley²⁰ report on a prolonged and late toxic reaction in a patient following the intravenous use of 10 cc. of sodium evipan. Mörl,²¹ a few months after the introduction of evipan, reports a fatal case and mentions three additional fatalities, one transient cardiac standstill, and 2 cases of collapse, the latter occurring after the administration of such small doses as 2 to 3 cc. These reports of toxic reactions indicate that while evipan is of distinct interest because of the short duration of its action, and under special indications may be of distinct usefulness, its intravenous administration for anesthesia is not without danger.

Recently, renewed attempts have been made to use the barbituric acids for the relief of pain and for the induction of amnesia *in labor*. Averett²² advocates the combined use of nembutal and scopolamin when labor is definitely established. Six grains of nembutal are given by mouth and 1/100 gr. scopolamin hydrobromid subcutaneously. The average duration of analgesia in 160 cases was $5\frac{1}{2}$ hours. No change in the respiration was noted. The blood pressure dropped 5 to 10 mm. The frequency and severity of uterine contractions were not interfered with. The first stage of labor either was not altered or was of shorter duration. The second and third stages were unchanged. In 110 cases complete amnesia was present, and in 42 cases there was some recollection. Maternal and fetal mortality did not occur. McGuinness²³ has

used nembutal because of the relatively short duration of its action in 140 cases of full-time confinement. A patient weighing 160 pounds received an initial dose of 6 gr. by mouth, followed by a second dose of 3 gr. within 3 hours, and by successive doses of 3 gr. every 2 or more hours until delivery. The capsules were administered on an empty stomach, with warm water. Rectal administration is also feasible. Fifteen minutes after the first dose the patient became drowsy and in 30 minutes she was sleeping between pains. During uterine contraction there were usually groaning, restlessness and partial awakening. Postoperative nausea and vomiting were not increased. Little or no interference with the course of labor was observed. Irving, Berman and Nelson²⁴ report their extensive experiences in the Boston Lying-In Hospital on the comparative efficacy of pantopon and scopolamine, pantopon and rectal ether, pernocton, sodium amytal, scopolamine and pentobarbital, scopolamine and sodium amytal, rectal ether and pentobarbital, and rectal ether, pentobarbital and paraldehyd. In each series, 100 cases were used with the exception of the sodium amytal and scopolamine series, which consisted of 160 patients. Pentobarbital and scopolamine was considered the most effective of any of the medications used. Absolute loss of memory was shown by 86% of the patients; incomplete amnesia by 14%. The only side effect was restlessness, which was frequently present. They advise against the use of pantopon and morphin during labor, as they delay the initial breathing of the baby.

The therapeutic induction of prolonged sleep by means of barbituric acids in patients with *psychosis* dates back to 1922, when Kläsi²⁵ advocated the beneficial effect of the repeated intravenous use of somnifen in certain psychoses. It has been claimed that such a prolonged sleep may aid in interrupting the course of a psychosis and so hasten recovery. Müller,²⁶ in 1925, reviewing the literature and his personal experiences on the intravenous use of somnifen in certain psychoses, mentions 15 fatalities as well as severe non-fatal intoxications during the treatment of 311 patients. The immediate cause of death was circulatory failure in 5 instances and pneumonia in 6; in 4 patients other etiologic factors were present, but somnifen was a contributing cause of death. There are two recent reports on the use of barbiturates in neuro-psychiatric conditions. Wagner,²⁷ summarizing his general clinical experiences, warns that if the drugs are given over a long period the histologic changes produced by the administration of large doses may lead to permanent functional impairment. Lorenz, Reese and Washburne²⁸ report on physiologic observations during intravenous sodium amytal medication in 350 patients with psychosis: an average of $9\frac{1}{2}$ gr. (14.3 cc. of a 5% solution) were required to obtain complete narcosis. The functional group of psychoses required a somewhat larger dosage than the organic group. Because of the great instability of the blood pressure in the involutionary group greater caution was required in this group.

The problem of *addiction* to barbituric acids has repeatedly been discussed in the literature. Gillespie,²⁹ summarizing the evidence, denies its occurrence. (The reviewer is inclined to agree, if addiction is restricted to habits associated with withdrawal symptoms. Morphin and cocain addicts, on the other hand, in case of insufficient supply or lack

of supply, often substitute barbituric acids. Psychologic habit formation to the barbituric acids is not uncommon.)

In view of the widespread clinical use of the barbiturates, as well as their recent rather frequent use with suicidal intent, *poisoning* is relatively common. The most frequent manifestations of intoxication, as is well known, are coma, disturbances of the heart regulation, and tendency to vasomotor collapse. In a recent review of the subject Gillespie²⁹ found no record in which barbiturates, either in single or in repeated smaller therapeutic doses, caused death in the absence of complicating factors. He has estimated that the ratio of safety with smaller therapeutic doses is 1 to 5 with veronal and 1 to 3 with luminal. Carrière, Huriez and Willoquet³⁰ summarize the histologic changes observed in man and in rabbits following fatal barbituric poisoning. Degenerative changes are described in the liver and kidney parenchyma, as well as disintegration of the cells of the central nervous system. Congestion in the lungs, with tendency to bronchopneumonia, was observed. A review of the literature up to 1929 is also presented by Lundy and Osterberg.³¹

That cutaneous rash may follow the use of even small amounts of certain barbiturates has been known since 1903.³² The recent interest in the relation of allonal to agranulocytosis has also raised the question of whether cutaneous hypersensitivity is caused by allonal (mixture of allyl-iso-propyl barbituric acid and amidopyrin and allurate [allyl-iso-propyl barbituric acid]). Unger³³ reports a patient who, after the ingestion of only one tablet of allonal, experienced swelling of the eyelids, cheeks and lips. Blotches appeared on the forehead, palms and backs of the hand. Crohn³⁴ has reported a case with repeated attacks of urticaria, and scrotal and genital edema after taking allional (a preparation similar to allonal). In a case reported by Loveman³⁵ exacerbation of an eruption was produced by allonal. Separate administration of allurate and amidopyrin showed that the cutaneous sensitivity was due to the barbituric acid and not to amidopyrin. Allyl-iso-propyl carbamid and numerous other barbiturates did not induce skin lesions. Other drugs producing fixed eruptions, such as phenolphthalein, antipyrin and amidopyrin had no effect. Passive transfer to hypersensitivity was unsuccessful. Patch, intracutaneous and scratch tests were all positive to allonal and allurate in previously active areas, but produced no reaction in normal skin areas. Thus in this case allyl-iso-propyl barbituric acid was definitely responsible for skin sensitivity.

Madison and Squier³⁶ claim that the "benzene chain derivatives" are probably responsible for primary granulocytopenia. From their data, however, one cannot ascertain whether the barbituric acid in addition to amidopyrin plays any rôle. Watkins,³⁷ reporting 32 cases of primary granulocytopenia, has observed 5 patients who had taken iso-amyl-ethyl barbituric acid or its sodium salt prior to the onset. All these patients died. Four patients with fatal outcome had taken sodium ethyl-methyl-butyl barbiturate. Two patients, one of whom died, had taken phenobarbital. As acknowledged by the author, the presented data simply suggest the possibility that certain individual idiosyncrasies of the white blood cell forming apparatus exist. Whether the barbituric acid derivatives can be directly responsible for agranulocytopenia is therefore not yet settled.

The *treatment* of severe barbituric poisoning, until very recently, has been unsatisfactory. The most promising recent method of treatment is based on strychnin and barbituric acid antagonism. Haggard and Greenberg³⁸ have shown in 1932 that phenobarbital sodium controls strychnin convulsions in rats and dogs. Animals have survived 5 times the fatal dose of strychnin. That the antagonism is a reversible one was shown by the fact that animals receiving 3 times the fatal dose of phenobarbital sodium have been saved with strychnin. Kempf, McCallum and Zerfas³⁹ have treated 11 cases of strychnin poisoning with sodium amytal and sodium pentobarbital, given intravenously, and claim that these substances were life-saving measures. Successful treatment of barbituric acid poisoning with massive doses of strychnin has been reported recently in France. Bertrand-Fontaine and Claass⁴⁰ have reported the case of a young woman who ingested 17 gm. of veronal and after being in coma received a total of 39 centigrams of strychnin by vein in 64 hours. A solution containing 3 mg. per cubic centimeter was used. Every hour during the day and every 2 to 3 hours at night doses of 9 to 15 mg. of the sulphate salt were given. Manifestations of strychnin poisoning were not observed and recovery followed. Eschbach⁴¹ reports a case with severe phenobarbital poisoning receiving 26 mg. of strychnin by vein within 2 hours. Instantaneous improvement with ultimate recovery followed. Denéchau and Bonhomme⁴² describe a female patient of 29, who had taken 6 gm. of phenobarbital, receiving a total of 48 centigrams of strychnin before recovery. Laignel-Lavastine and Bidou⁴³ describe recovery in a case with severe dial poisoning. The patient was in coma for 30 hours when an initial intravenous dose of 20 mg. of strychnin was given, followed by a second dose of 10 mg. in 1 hour, and then 10 mg. every 2 hours and 2 injections every 3 hours. The last injection was 10 mg., 10 hours later. The patient recovered. Additional cases of the strychnin treatment of barbituric acid poisoning have been reported.^{44,45,46}

SOMA WEISS.

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RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION ON ROENTGENOLOGY, MAYO CLINIC,
ROCHESTER, MINN.

PULMONARY TUBERCULOSIS.

IN the opinion of Sampson and Brown, thoracic surgery has attained the advanced position it has today solely because of the precise diagnosis of the extent of the pulmonary lesion which is made possible by roentgenologic study. Roentgenograms of the lung may be likened to pulmonary biopsy, and although histopathologic study of any given lung is limited of course to disclosure of a single state, in a series of roentgenograms one has the diagnostic equivalent of serial biopsies of lesions in a state of flux. Such studies have greatly helped to banish ennui from sanatoriums.

Physical methods of pulmonary diagnosis cannot safely be neglected. However, primary infection in infancy and childhood that produces a small patch of bronchopneumonia cannot be diagnosed by physical signs; the condition is rarely detected save by accident, and roentgenologically it can be detected only at such time as it has apparently become healed and calcified or ossified. The same thing is true of the associated changes in the tracheobronchial lymph nodes; such changes also entirely escape detection by physical examination and are not seen roentgenologically until such time as they project their shadows into the high light of the bronchus or into the normal roentgenologic field. D'Espine's sign has been shown by roentgenographic study to be of no value. The importance of the discovery of the primary infection is attested by the thousands of dollars spent during the last one or two decades for roentgenologic investigation, which alone is capable of localizing in the lung an infection suggested by a positive tuberculin test. Physical signs tell little of what happens in tuberculosis of the lungs during that period when the disease exacts its least toll of human life, the interval between primary infection and the development of definite pulmonary tuberculosis.

Sampson and Brown felt that roentgenology has given some proof that the adult type as a rule does not arise directly by extension from the primary lesion. If by the age of 23 there are no parenchymatous changes in the lung suggestive of pulmonary tuberculosis, only in rare instances will pulmonary tuberculosis develop. No child should be allowed to leave school, particularly high school, until roentgenologic examination of the thorax has been made. In Sampson and Brown's experience with 4000 examinations, conducted over a period of 7 years, only 7 of 79 children with parenchymal lesions had definite physical signs on examination. The roentgenogram revealed that the usual site

of beginning, clinical pulmonary tuberculosis was in the upper lobe below the clavicle. Of 280 patients with minimal pulmonary tuberculosis, râles were present in the apex in 27%, whereas a definite parenchymatous lesion was revealed roentgenologically in more than 99%. Hemoptysis was as frequent as râles (26%), whereas pleuritic effusion occurred in 12% of cases. Bacilli of tuberculosis were found in 35%. In a series of 1004 consecutive cases studied, there were no patients with definite physical signs and a negative roentgenogram. In 19 cases the physical signs suggested greater extent of the lesion than did the roentgenogram. In 211 cases the extent of the lesion appeared to be the same by both methods. In 361 cases the roentgenogram revealed more extensive disease than was inferred from the physical signs. In 396 cases the roentgenogram gave definite evidence of pulmonary tuberculosis, whereas the physical signs were practically normal. In 392 cases in which a cavity was revealed in the roentgenogram, physical signs of the cavity were present in only 58 (15%). Sampson and Brown placed great significance on the roentgenogram in determining the prognosis of pulmonary tuberculosis. Willis asserted that pneumonic consolidation that involves a comparatively large portion of a lobe, or even an entire lobe, is particularly prone to appear among children. It is the general impression that these consolidated areas definitely occur more frequently than would be expected if they were caused by the pneumococcus, that is, that they are encountered more commonly among tuberculous patients than among people in general. Usually the consolidated areas under consideration have been attributed to one of the following causes: atelectasis, edema, pneumococcal pneumonia, non-specific pneumonia in tuberculous individuals, known as "epituberculosis," and tuberculous pneumonia. The term, atelectasis, is loosely used by some; certain physiologists and experimental physiologists assert that there can be no true atelectasis, short of that involving an entire lobe, unless it is brought about by the diseased alveolar walls which act as barriers to the air in neighboring air spaces. Physical examination is usually quite different in pneumonic consolidation and in massive collapse, and is highly characteristic in each condition. Willis felt that edema has little to do with the formation of the characteristic roentgen shadows. Pneumococcal pneumonia occurs only rarely among patients in sanatoriums.

That a peculiar nonspecific pneumonic consolidation may occur in tuberculous patients (and in these only) is the contention of Eliasberg and Neuland, who gave the affection the name, epituberculosis. The only criteria for ordinary pneumonia which these consolidated areas offer are the physical signs of consolidation. Several points make the diagnosis of tuberculosis highly probable if not mandatory. These are: (1) the long duration, (2) the lack of stormy symptoms, (3) the necessary presence of tuberculous infection, as evidenced by the tuberculin reaction, (4) the presence of bacilli of tuberculosis in the sputum, as demonstrated in numerous instances, (5) the histologic appearance of excised pulmonary tissue in a clinical case, and (6) the reappearance of the condition in children after injection of tuberculin. The considerable volume of experimental work of others and their own experimental data indicates that tuberculous pneumonia may be induced in experimental animals. This disease frequently undergoes resolution, as is

evidenced by serial roentgenograms and at necropsy. It is clear that this pneumonia of animals is specifically tuberculous in nature. It is likely that such specific pneumonic processes are very similar to, or identical in nature with, clinical pneumonic consolidations that occur in tuberculous individuals, and that each is the product of the exudative, allergic reaction of an animal organism which is sensitive to bacilli of tuberculosis and tuberculin.

Allison and Medelman presented a study based on observations of a series of thoracic roentgenograms of tuberculin-tested children made over a period of years. The series embraced more than 10,000 children many of whom were reexamined roentgenologically over a period of 10 years. Allison and Medelman's classification of first infection tuberculosis in childhood is: (A) known infection with no demonstrable lesion, (B) uncalcified tuberculosis of the primary pulmonary or childhood type, (C) calcified tuberculosis of the primary pulmonary or childhood type, (D) adult type tuberculosis with or without a demonstrable primary focus. In considerably more than half of the cases in Group A in which the Mantoux reaction was positive, no lesions in the thorax attributable to tuberculosis were demonstrated. In Group B the primary focus is situated in any part of either lung and is in the form of tubercles. Occasionally it may be bilateral, its size varying within wide limits. In unfavorable cases the primary focus may break down with formation of a cavity. Various complications caused by the dissemination of the tubercle may occur. Allison and Medelman have observed cavitation, miliary tuberculosis, bone tuberculosis, and tuberculous enteritis which developed during the evolution of an uncalcified pulmonary lesion of the first infection type. These complications, however, were extremely rare. The typical roentgenologic appearance is that of a homogeneous, dense opacity which involves a lobe, or a roughly triangular portion of a lobe with the base of the triangle toward the periphery. Quite frequently the hilar and mediastinal lymph nodes draining this region can be visualized as a separate lobulated mass. The density of the infiltration decreases, and finally completely disappears, at about the time the calcified deposits fuse into one or more dense Ghon tubercles. As regression of the parenchymal lesion occurs, calcium is deposited in the involved lymph nodes. The most frequent lesion simulating resolving parenchymal tuberculosis is pneumonia. If the roentgenologist cannot be sure of the differential diagnosis at the original examination, he may take another roentgenogram in a week or 10 days; if the lesion is unchanged, the diagnosis is obvious. It is very important from a clinical standpoint to differentiate adult and childhood types. This is done by: (1) the well-known appearance of the adult type of infection, usually in the upper half of the lungs; (2) previously existing calcification of a former primary infection; (3) the presence of enlarged nodes in the childhood type and their absence in the adult type, and (4) if necessary, prolonged observation. Tuberculosis of childhood has a tendency to improve and to calcify, whereas adult tuberculosis tends to increase without calcification.

Primary tuberculous involvement of the tracheobronchial lymph nodes may occur without a demonstrable pulmonary focus. The diagnosis in such cases depends on actual visualization of a rounded density or lobulated mass extending into the parenchyma of the lung from the

hilus or mediastinum, or both. From infancy to the age of 18 years it will not be seen in more than 4 or 5% of all cases. About 25% of the children with a positive Mantoux reaction fall into Group C. The discovery of calcified deposits gives definite evidence of the tuberculous nature of the lesion, except in rare instances. The adult type of tuberculosis occurs on reinfection of those children who have previously been sensitized by a childhood type of infection. At least 50% of all children with the adult type of tuberculosis have it superimposed on a demonstrable childhood tuberculosis.

Pinner stated that the hematogenous (nonmiliary) type of pulmonary tuberculosis seems to be little known. On account of its atypical manifestations, it is frequently not diagnosed. It has been described in the literature quite frequently, mostly in the form of reports of cases and under a great variety of names. A discussion of the literature would not particularly help to clarify the matter as it stands. Of Pinner's 28 reported cases, 14 came to necropsy. Roentgenologically the disease is characterized by multiple, small foci which are usually more or less symmetrically distributed throughout the fields of both lungs. The distribution may be more or less even, or it may be limited to certain parts of the lungs, usually to the upper parts. The clinical symptoms and physical findings are often in great disproportion to the amount of roentgenologically demonstrable involvement. The further development of these lesions reveals certain well-defined characteristics that distinguish them clearly from bronchogenic tuberculosis. This type is assumed to be due to a hematogenous spread, or to repeated ones, for the following reasons: (1) the more or less even distribution of the lesions, (2) the frequent absence of older pulmonary foci from which a bronchogenic spread could have occurred, and (3) the frequent association of extrapulmonary lesions with the pulmonary lesions. The major morbid processes take place within the interstitial structure of the lung. These patients have little sputum and rarely with bacilli; the appearance of bacilli in the sputum indicates small ruptures into the canalicular system of the lung.

Watkins, discussing the healing of cavities in pulmonary tuberculosis observed roentgenologically, remarked that it was a clinician who asserted that only 60% of cavities were found by physical examination whereas 95% of them were revealed by roentgenologic examination. The majority of critical observers accept as substantially correct Graeff's statement (1921) that the development of a pulmonary cavity is a death sentence for the unfortunate patient. This statement is subject to many exceptions. A tuberculous patient with a cavity as large as 1 inch in diameter has an average life expectancy under treatment of only 1 year. Probably half of the patients can be healed by simple or modified rest in bed. For another fourth the cavity can be closed by pneumothorax. The remaining fourth will require the assistance of a thoracic surgeon for such procedures as phrenicectomy, intrapleural and extrapleural pneumolysis, and thoracoplasty. Roentgenologic study offers the only certain means of determining whether a cavity is enlarging or healing under treatment.

Bruck, in describing a round foci type of pulmonary tuberculosis, stated that Straub (1932) wrote a comprehensive article analyzing all cases reported up to that time. Straub found no reference to this type

of tuberculosis in the American literature. Six to 8 isolated cases were reported in the German literature and Straub described 10 cases seen at his clinic. This form of tuberculosis occurs as round foci in a thorax that has other definite and characteristic lesions, or these foci may be the only evidences of the disease. The lesions can be detected only by Roentgen rays, they are usually quiescent, and many times they produce no symptoms but are often detected accidentally during the course of other roentgenologic studies. Roentgenographically, over a period of years, the lesions do not appear to have undergone any definite change. Clinically, most of the patients are afebrile, have no constitutional reactions, and feel no discomfort. In Bruck's case the sputum was positive for bacilli of tuberculosis. On biopsy, tuberculosis of the right vocal cord was found. A small minority of the cases reported clinically gave evidence of activity.

Murphy, in discussing bronchography as an essential and safe adjunct in the study of pulmonary tuberculosis, reviewed the history of the application of bronchography to the study of bronchiectasis and pulmonary tuberculosis and described the technique employed. The study combined roentgenoscopy and roentgenography. Ninety-nine injections of lipiodol were made in cases of pulmonary tuberculosis in which there were no major complications. Bronchial dilatation was observed in 60% of 65 cases, ranging from infiltrating to fibrocavernous lesions. Variability in the association of bronchial dilatation and tuberculosis was noted. Bronchial dilatations of all types and extent, which could not be distinguished from parenchymal lesions in the ordinary roentgenogram, were clearly defined in the bronchogram.

Neuhof considered bronchography an essential measure for the precise localization of the lesion and delineation of the part of the pathologic process in pulmonary tuberculosis, when surgery is indicated, just as experience has taught it is in pulmonary abscess. When cavities are formed, a small fluid level has been the maximal direct evidence of those in the upper lobe; the bronchogram adds indirect evidence by delineating the disposition of the bronchi and bronchioles around the site of cavitation, usually about its lower circumference, outlining its situation and shape. Areas of rarefaction in the roentgenogram have been identified as cavities in the bronchogram. Bronchiectasis in the pulmonary parenchyma about the cavity can usually be differentiated. Bronchiectasis in the lower lobe is often revealed as a grossly abnormal bronchial tree, whereas in the roentgenogram it appears only as a slight abnormality. Bronchography is of great value in estimating the degree of fibrosis and retraction in the tuberculous lobe; it may avoid some futile operations on the phrenic nerves and not a few ineffective pneumothorax treatments. It has also been found useful in the demonstration of the results of the mechanical treatment of pulmonary tuberculosis.

MISCELLANEOUS LESIONS OF THE LUNG.

Bendove and Gershwin discussed the inverse ratio in roentgenologic visualization of the bronchi and alveoli after the injection of contrast mediums. When iodized oil is injected intratracheally, it tends to delineate the bronchi and alveoli in an inverse proportion, that is, the more the alveoli are outlined, the less the bronchi are visible, and *vice*

versa. This inverse ratio in visibility of the iodized bronchi and alveoli is of diagnostic significance. In a normal lung the outlined alveolar element predominates, overshadowing all the bronchi, and the roentgenographic image simulates a tree when abundant leafage covers all the branches. Diseased and dilated bronchi retain most of the injected material, and only very few if any of the alveoli in the corresponding region will be delineated in the roentgenogram. In cases of extreme cylindrical dilatation, the filled bronchi resemble branches of a tree devoid of all remnants of former foliage. The absence of the alveolar "leaves" may be general or localized, depending on the extent of the bronchial dilatation. Any bronchus that retains lipiodol 15 minutes after injection is to be considered functionally impaired, irrespective of its morphologic appearance. In order to maintain definite standards of comparison, it is always advisable to inject 20 cc. of lipiodol and to outline only one lobe at a time.

Glass, in a series of illustrations, outlined the bronchopulmonary segment with special reference to putrid pulmonary abscess. In its primary evolution, an abscess involves definite and circumscribed regions of the lung. These regions are subdivisions of pulmonary lobes and constantly possess a definite shape, size, and position in the thoracic cavity. Each is composed of a bronchus and its associated alveolar tissue. The bronchus is one of the main divisions of a lobar branch, and each segment is a potential zone of infection through aspiration. Each segment is named according to its position in the thoracic cage and the pulmonary architecture. The postero-anterior roentgenogram affords the clearest view of the lung and always reveals shadows of abscesses to the best advantage.

Van Allen, La Field, and Ross defined atelectasis as that state of the lungs as a whole, or of any part, in which there is complete "airlessness" and alveolar collapse; it is "massive" when the area involved was large enough to permit the consistency of its Roentgen shadow to be determined, and "focal" when the area was not so large. Massive atelectasis was produced in several dogs by plugging a lobar bronchus for 24 hours. The animals were killed, the lungs removed, and roentgenograms were made of both the normal and the atelectatic lobes. The atelectatic lobes were reinflated and roentgenographed again. Specimens of human lungs were obtained at necropsy, roentgenographed, and the nature of the lesions checked by gross and histologic examination. Roentgenograms of the thorax of living subjects presenting similar lesions were collected. The pulmonary shadows in the three groups of roentgenograms so obtained were studied and compared. Only when the tissues are entirely free from infiltration with air is their shadow homogeneous. "Ground glass" best describes the appearance of the Roentgen shadow.

In clinical roentgenography, if the diaphragm is examined at expiration as well as at inspiration, elevation of the diaphragm on the side of the lesion should occur in atelectasis at both phases of respiration, whereas in pneumonia it occurs, if at all, at inspiration only. Focal atelectasis presents scattered mottlings, cloudings, and streaks which correspond to the positions of the individual foci of alveolar collapse; the ground-glass sign is absent. Focal atelectasis occurs in pure form most frequently in the compressive and congenital types of the disease.

The markings tend to be arranged in lines radiating from the hilus. The majority of cases of postoperative atelectasis are of the focal form. The Roentgen shadow of a pneumonic area of lung is practically always heterogeneous in composition because of the air which is scattered through the lesion; even at the height of the disease careful scrutiny discloses faint cloudings or mottlings rather than a completely uniform and ground-glass shadow. The same applies to tuberculosis. Hemorrhagic infarction is almost always heterogeneous in consistency owing to the presence of smaller or larger amounts of air in the tissues. Neoplasms present the ground-glass sign, but in pure form they are readily distinguished from massive collapse by the absence of the environmental displacement that characterizes the latter disease. In extrapleural masses, the viscera adjacent to the lungs are either not displaced at all or are displaced in a different direction than in atelectasis. When massive atelectasis and other consolidative disease occupy the same portion of the lung, the ground-glass superimposed shadow obliterates all marks of the other lesions.

CHARLES G. SUTHERLAND.

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ORIGINAL ARTICLES.

CHRONIC CONGESTIVE SPLENOMEGALY AND ITS
RELATIONSHIP TO BANTI'S DISEASE.

BY RALPH C. LARRABEE, M.D.,
CONSULTING PHYSICIAN, BOSTON CITY HOSPITAL,
BOSTON, MASS.

WHEN a patient is admitted to the wards of a hospital with an enormous spleen, anemia with leukopenia and perhaps a history of gastro-intestinal bleeding, the tentative diagnosis is likely to be Banti's disease. Many such cases have been treated—and with much success—by splenectomy. If, however, the patient is a confirmed alcoholic, or if further research discloses evidence of cirrhosis of the liver or some other intra-abdominal abnormality, the splenomegaly is apt to be attributed to *that*. In the resulting doubt and confusion the patient will probably lose the benefit of an operation from which he might have obtained great relief. For there is a prevalent impression that only Banti's disease (and not splenomegaly due to liver cirrhosis) should be treated by splenectomy.

Banti's disease, though frequently diagnosed in the ward, is, if Banti's right to define the disease that bears his name is respected, extremely rare on the autopsy table. Strictly adhering to Banti's classical description,^{1,2} the patient must have progressed through certain definite stages, the spleen must show certain and none too perspicuous histologic changes and, above all, there must be no obvious etiologic factor. So rare are the cases that fill all of these requirements, both positive and negative, that most of them emerge from the pathologic laboratory labeled cirrhosis of the liver or perhaps classed on some other equally definite etiologic basis. And the Banti pigeon-hole remains nearly, if not quite, empty!

Waiving, for the moment, any consideration of the underlying nature and pathogenesis of Banti's disease, let us consider the clinical syndrome upon which the diagnosis must be based, before operation or, at least, before autopsy. In thus freeing our definition from any limitation on the basis of etiology, it must be realized that we are admitting many cases which are not Banti's disease at all under the definition which he gave to it. The picture includes both positive and negative aspects. On the negative side one must, by appropriate studies, have excluded such definite diseases as leukemia and aleukemia, hemolytic jaundice and certain cases of primary hypochromic anemia. On the positive side we must have, first, a large spleen, usually large enough to be palpated with ease and sometimes reaching to the umbilicus or lower. Many patients have hemorrhages from the stomach, esophagus or bowel and late in the disease ascites is common. Second, the blood will show anemia, except possibly in very early stages, usually hypochromic in type, with more or less leukopenia and frequently a mild thrombocytopenia. Third, if the spleen is removed it will show, histologically, cellular hyperplasia, fibrosis (Banti's "fibro-adenie") and generally also congestion.

The writer has adequate records of 47 cases showing this picture. All had large spleens. Gastro-intestinal hemorrhages occurred in 25. Ascites was present in 25. The blood showed more or less anemia in 44. Although in an occasional count the color-index was greater than unity, the blood picture was invariably recognized as that of "secondary" or microcytic anemia. Leukopenia was present at one or more blood examinations in 38 cases, usually in all counts where there was no complication tending to produce leukocytosis. Platelets were likewise numerically decreased in 23 of the 42 cases in which this point was noted.

Opportunity for microscopic examination of the spleen was afforded in 31 cases, as a result of operation or autopsy. Nearly all of these spleens were studied by Dr. F. B. Mallory and his assistants. The reports were almost monotonously uniform. Fibrosis was invariably present, though in varying degrees. Usually there was more or less vascular congestion. As this paper is not a pathologic study, further consideration of the histologic details will not be attempted. It need only be said that the changes found in these spleens were such as might be fully accounted for by long-continued passive congestion. A few cases of leukemia and especially of Hodgkin's disease, the clinical features of which resembled in some respects those of Banti's disease, have been excluded.

The records of these cases have been analyzed in an effort to determine what other lesions, if any, coëxisted with those already described, with an especial view to such lesions as might of themselves cause obstruction to the venous outflow of the spleen. The results are summarized in the table,

TABLE 1.—ANALYSIS OF CASES OF CHRONIC CONGESTIVE SPLENOMEGALY.
Splenectomy.

	Total.	Not operated upon.	Died of oper- ation.	Relieved.	Not relieved.
Alcoholic cirrhosis	9	4	2	2	1
Toxic cirrhosis	3	1	2
Syphilitic cirrhosis	5	2	2	..	1
Cirrhosis of undetermined type	7	3	..	3	1
Non-cirrhotic liver abnormalities	2	1	..	1	..
Adhesions	5	2	1	2	..
Congenital heart abnormality	1	1	..
Ptosis of spleen	1	1	..
Etiology unknown	14	10	..	4	..
Totals	47	23	7	14	3

In 14 cases no obvious cause of portal obstruction was found. These were mostly the cases in which neither operation nor autopsy was done (Cases 1 to 10 inclusive). Perhaps they should have been omitted because, without opening the abdomen, most obstructive lesions other than the exceptional ones involving enlargement of the liver will be missed. A large liver may, of course, bear an obstructing lesion, but is less apt to do so than is the much less easily recognizable liver which is decreased in size.

Two of the 14 negative cases (Nos. 11 and 12) were operated upon; but the records are silent as to the presence or absence of abnormalities of the liver and other viscera.

Only 2 other cases failed to show some significant abnormality in addition to the splenomegaly. (See abstracts of Cases 13 and 14.) It is possible that the liver of Case 14, as in a case reported by Fox,⁴ was actually diseased, although at operation it appeared to be normal. Since in neither of these cases any especial attention was paid to the condition of the portal and splenic veins, they can hardly be taken as evidence that the splenic fibrosis was the primary lesion. Unfortunately, neither the surgeon in exploring the abdomen nor the pathologist in performing an autopsy includes a careful study of these veins as a part of his regular routine.

In 24 (73%) of the remaining 33 cases, some form of cirrhosis of the liver was considered to be present, this conclusion being based on purely clinical evidence in 4 cases, on operative exploration in 9, and on microscopic examination of liver tissue in 11. Efforts to group these cirrhoses according to Mallory's classification⁵ were not always successful, since several were so atypical that they could not be placed, even though the entire liver was available. However, at least three types of cirrhosis—alcoholic, toxic and syphilitic—were recognized beyond reasonable doubt.

The 9 cases of alcoholic cirrhosis (Cases 15 to 23, inclusive) included 3 diagnosed microscopically and 4 recognized at operation. One of the cases autopsied also showed hemochromatosis (Case 16) and one of those palpated at operation (Case 18) had

dense adhesions about the liver. In 8 of the entire 9 the patients gave histories of alcoholism, and the 1 that did not (Case 20) showed at operation a large and "finely irregular" liver.

The 3 cases of toxic cirrhosis (Cases 24, 25 and 26), the "healed acute yellow atrophy" of Mallory, were especially interesting. No case was accepted as belonging in this group unless the diagnosis was definitely proven by histologic examination of the liver. The writer believes that such cases are not uncommon and it is probable that some of the cirrhoses here included in the unclassified group were of this nature. They all had fibrotic spleens and clinically were quite as suggestive of Banti's disease as the others.

The 5 cases (Nos. 27 to 31 inclusive) classed as syphilitic cirrhosis offered considerable difficulty. All had positive Wassermann reactions (1 became negative after prolonged treatment). Nevertheless one may not assume that any abnormal liver in a syphilitic is syphilitic cirrhosis. However, in 2 cases (Nos. 27 and 30) the liver was examined microscopically and characteristic lesions were found. Two of the 5 cases showed, in addition to syphilis, other lesions which might have been influential in causing portal congestion—one (Case 29) had a cancer of the uterus, another (Case 27) had dense perihepatic adhesions. Case 28 may have had hemolytic jaundice, although he was definitely syphilitic and both the blood picture and the general clinical findings were characteristically of the Banti type.

Cases of syphilis with splenomegaly and anemia have been reported by Giffin.⁶ It is interesting to note that, in his patients, while antisymphilitic treatment led to general improvement, it did not benefit the anemia nor did the spleens decrease in size. Splenectomy, however, did result in more or less striking improvement in the blood. The inference appears to be that the splenomegaly and the anemia were results, not of active syphilitic disease of the spleen, but rather of portal obstruction from syphilitic changes in the liver. Antisyphilitic treatment, while relieving the active disease in that organ, did not result in the disappearance of residual fibrotic changes nor the consequent interference with the flow of blood through the portal channels. But just this relief of the portal circulation was accomplished by removal of the spleen.

There were 7 cases of cirrhosis of undetermined type (Cases 32 to 38 inclusive). Marked evidence of a cirrhotic process was found in all of them, being based on autopsy material in 3, on biopsy in 1 and on palpation at operation in the others. All 3 of the cases in which the diagnosis was based on operative exploration had notably small, hard livers; in 1 (Case 35) the liver was surrounded by dense adhesions, possibly the result of acute abdominal suppurative disease; in another (Case 38) the liver was so irregular and scarred as to suggest toxic cirrhosis. Of the autopsied cases, 1 (Case 32) showed old portal thrombosis and a liver the gross appear-

ance of which suggested toxic cirrhosis; in another (Case 36) there was clean-cut portal cirrhosis; in a third (Case 33) the liver was possibly syphilitic; but in none was the pathologist able to state the type with certainty. This group is unsatisfactory only because the cases could not be classified etiologically. There is no evidence warranting the assumption that they were representatives of "true Banti's disease." Not only were the findings decidedly divergent, but in several of them, to say the least, the evidence is decidedly in favor of primary origin in the liver rather than in the spleen.

Cases 39 and 40 had enlarged livers and were classed as "non-cirrhotic liver disease." In neither was there any evidence as to the nature of the enlargement. A better classification would perhaps have been "liver abnormalities of undetermined nature."

Of the 5 cases (Nos. 41 to 45, inclusive) considered to be the results of adhesions about the portal area, the stories of all included operations for appendicitis. In Case 45 the diagnosis was presumptive. In all the patients whose abdomens were explored there were dense adhesions about the liver and generally also about the spleen. Clinically these cases did not differ from the others, except perhaps in the unusual completeness of recovery in the 2 that survived splenectomy. In addition to these cases classed as due primarily to adhesions, a number classed in other categories also had adhesions about the liver (Cases 11, 12, 18, 19, 27 and 35). To what extent the adhesions were responsible for the portal congestion it is impossible to say.

In Case 46, the only finding that could account for portal congestion was a cardiac abnormality considered to be congenital. He was greatly improved after splenectomy and the blood slowly returned to normal figures. When last heard from he was working as a janitor and boiler tender.

Finally there was 1 patient (Case 47) with marked ptosis of the spleen, which was palpated in a position so low that it was mistaken for a uterine fibroid. Although there was no pre-operative study of the blood, the spleen was fibrotic. She continued to present a mild microcytic anemia which slowly cleared. A somewhat similar case was reported by Pernet.¹⁴

Results of Splenectomy. Of the 47 cases upon which this paper is based, 24 were splenectomized. Seven of these died within a few days (29%). This seems unduly high. It must be remembered, however, that most of the cases were derived from the unfavorable material of a large municipal hospital. An unusually large proportion were in the more advanced stages of the disease, as shown by the fact that 11 (46%) had already had hemorrhages and 12 (50%) were ascitic. Several operations were distinctly of the last-resort type.

On the other hand, practically all of these patients had underlying lesions in organs other than the spleen, lesions which splenectomy

would rarely eradicate. Hence for most of them splenectomy was but a palliative operation. Believing it to be such, it has not always been advised in early cases where the patients were not yet materially incapacitated. This in spite of the fact that the operative mortality is most favorable in early operations. Years ago Osler,⁸ speaking of splenic anemia, stressed its extreme chronicity. Some of his cases which seem closely related to the ones here reported lived in fair comfort for over a decade. This is especially true of those patients with alcoholic cirrhosis whose habits can be controlled. It is perfectly proper, then, to postpone operation until it is needed. But such a course, however advantageous to the patient, is not beneficial to one's statistics.

In a previous paper dealing with splenectomy, the writer⁹ commented upon 2 patients (Cases 13 and 20 of the present report) who died of infections, in 1 probably septic endocarditis and in the other appendicitis, a few months after splenectomy. To these must now be added another (Case 14) who died of appendicitis after 2 years. A death from septicemia 2 years after splenectomy was reported by O'Donnell.²⁰ Such occurrences are not easy to account for. There is evidence that in rats and other animals splenectomy does increase the susceptibility to infection with *Bartonella*.¹¹ But, so far as the writer is aware, no similar increase in susceptibility to infection has been demonstrated in any other condition. It has been suggested that the anemia observed by Pearce, Krumbhaar and Frazier¹⁰ both in dogs and man after splenectomy may be the result of infection, but there is not the slightest evidence that such is the case, either in their studies or in this series.

Of the 14 other splenectomy patients, 1 (Case 34) is reported to have died of acute nephritis 2 months after operation; 1 (Case 27) died in 16 months of hematemesis; another (Case 21) died of cerebral hemorrhage after 7 years. It is impossible to say to what extent the operations were responsible. Four patients were not heard from after leaving the hospital. The remaining 7 were reported well after periods varying up to 7 years after splenectomy.

As to the specific benefits to be anticipated from successful splenectomy, it may be said that, of those who survived operation, but 3 (Cases 18, 27 and 34) failed to show at least temporary improvement. Of 11 patients with gastro-intestinal hemorrhage, 2 died of operation, 7 were completely and 1 partially relieved of this symptom. Of 12 patients with ascites, 4 died of the operation and 5 were relieved of the symptom. Of the patients operated upon, 23 were anemic before splenectomy; of these, 7 died of the operation, 9 were more or less completely relieved of this symptom, 5 partially relieved, 1 not relieved and in 1 continued hemorrhage and repeated transfusions confused the picture. It is probable that the degree of relief was greater than these figures indicate, for the anemia often improves but slowly and the follow-up of several cases was incomplete.

The table shows the relative results of splenectomy and the relative mortality in the different groups classified etiologically. The number of cases, when thus subdivided, is too small to have much significance. The writer has the impression that the toxic cirrhosis group is particularly unpromising, while in those in which the lesion is largely mechanical and non-progressive, splenectomy seems to be especially beneficial.

Comment. Are any or all of these cases properly classed as Banti's disease? Certainly if one takes Banti's own definition as a criterion they are *not*. He clearly recognized the occurrence of secondary cirrhotic changes in the livers of many of his cases, but with equal clearness he excluded cases in which the cirrhosis was primary. While admitting his ignorance of the true underlying cause of the disease, he supposed it to originate within the spleen, a splenogenous irritant carried through the portal channels being the cause of the phlebitic and sclerotic vascular changes as well as of the cirrhosis.

In attempting to explain the present series of cases it is needless to appeal for aid to this purely hypothetic toxin. It would seem most improbable that one and the same irritating agent, whether derived from the spleen or from the alimentary tract, would result in lesions so fundamentally different from one another as acute yellow atrophy and alcoholic cirrhosis (using this term in its purely histological sense). Moreover we find exactly the same clinical picture and exactly the same splenic abnormalities resulting from such purely mechanical causes as obstructing adhesions, congenital heart disease and ptosis of the spleen—and all about equally susceptible of improvement after splenectomy.

We are forced to the conclusion that most, if not all, of these cases were not only associated with lesions interfering with the outflow of blood from the spleen, but were actually the results of such lesions. So far as the effect upon the spleen is concerned it seems to be immaterial where the obstructing lesion is located: it may be in the liver, in the splenic vein, in the portal vein above the junction or even in the heart. Apparently it must be a long-continued *chronic* obstruction, for Warthin⁷ was unable to produce permanent enlargement of the spleen by ligating the splenic vein. Few cases of congestive heart failure last long enough. In 3 of the cases here recorded, symptoms followed 5 or 6 years after severe appendicitis. This would appear to be about the minimum.

There is little that is original about this concept. Warthin,⁷ in 1910, and Johnston,¹⁷ in 1931, expressed quite similar views. Many authors have described cases of alcoholic cirrhosis with splenomegaly showing close clinical resemblances to Banti's disease. Similar clinical states have been observed in syphilitic disease of the liver^{6, 19} in ptosis of the spleen,¹⁴ in primary obstructive disease of the portal vessels^{7, 15, 21} and in persistence of an open umbilical vein.¹⁸ Not a few observers have doubted the existence of such

an entity as Banti's disease and speak instead of Banti's *syndrome*. It is true that but few have been willing to come out squarely and unequivocally with this opinion. Thus, McNee,³ criticizing Banti's later view, states that Banti's disease is merely an unusual type of "ordinary alcoholic cirrhosis, in which high portal pressure and changes in the spleen precede the onset of marked fibrotic changes in the liver." This is clear enough, but he adds that the term Banti's disease should be given up and the cases classed either as hepatic cirrhosis or as splenic anemia, thus merely substituting for Banti's disease the even more indefinite term, splenic anemia. The writer of the present paper has never seen a case conforming in all respects to Banti's requirements, but he does not on this account deny the possible existence of such a condition. He believes, however, that a more general appreciation of the fact that the symptom complex common to all of these various conditions may result from the state designated in the title of this paper will conduce to much clearer thinking.

A clue to the possible relationship between these cases and those of Banti might perhaps be obtained by study of the microscopic lesions, a study which the writer is not qualified to undertake. The specimens are preserved and it is hoped that they will be studied by someone more competent. Here it is only necessary to repeat that the changes found in these spleens were, in the opinion of the pathologist, due to long-continued passive congestion. It is perfectly conceivable that a primary vascular splenitis may occasionally occur with lesions which might produce similar clinical results from circulatory obstruction within the organ itself. Therein possibly lies the connecting link between Banti's disease and such cases as those described in this paper. But this is, at present, pure hypothesis.

That the anemia and other features of the blood picture are consequences of changes within the spleen is quite generally admitted in view of their almost uniform improvement after splenectomy. When one looks at microscopic sections of these spleens the striking feature is the increase in connective tissue. Yet when one takes into consideration the very great size of the organ he is impressed with the fact that there must also be a very considerable increase in the pulp. Perhaps there is such a thing as "hypersplenism." Or the anemia may be in some manner connected with the divergence of the portal blood, including that from the digestive tract, as well as that from the spleen, away from its normal course through the liver into the gastric, esophageal and other vicarious channels. The degree to which the portal blood may be thus diverted has been pointed out by McNee³ and is much greater than is generally realized. In advanced cases of cirrhosis from 85 to 100% of the blood may find its way through collateral vessels. In such cases the metabolic products originating in the intestines and ordinarily carried directly to the liver can only reach the cells of that organ

by way of the much-dilated hepatic artery, after passing through the general circulation. However this may be, splenectomy relieves the blood abnormalities quite as regularly in the cases under discussion as it does in typical Banti's disease.

On the whole, this group of cases seems to be so distinct from those described by Banti—or perhaps we should say from Banti's conception of the cases he described—that it seems best to segregate them under a distinctive name. Yet the writer holds a sneaking suspicion that Banti would have classified some of the cases here described as primarily splenic, while the writer himself would have doubtless classed some of Banti's cases as primarily hepatic or portal. Banti's indefinite and confusing limitations have been commented upon by many writers—with especial clearness and force by Epplen.¹² We should not allow these and his hypothetical explanation to blind us to the fact that the clinical picture which he described has a much broader etiologic basis than he thought. Nor should we allow a patient to suffer needlessly just because we are not ignorant of the etiology of his ailment and can attribute it to a well-known cause.

It is believed that these results demonstrate that a considerable number of cases of splenic anemia dependent upon various lesions obstructing the portal blood flow may be relieved by splenectomy. At the same time the study demonstrates the futility of expecting to "cure" more than a very small proportion by this or any other means. However great and lasting the betterment may prove to be, it is only in those few cases where the obstructive lesion is confined to the spleen or the splenic vein that splenectomy gets rid of the underlying lesion. In a large majority of the cases, particularly the liver cirrhoses, the primary disease remains, and if it is of a progressive nature it goes merrily on. In cases where the underlying disease is far advanced the improvement in the blood and the partial relief of portal congestion can hardly be expected to restore the patient to a high degree of health.

The practical question concerns the choice of cases for splenectomy; and the practical answer is that we should "make the pathologic condition of the spleen and its effects on the blood the criterion" rather than the underlying cause (Mayo¹³). The physician or surgeon confronted with an actual case need not trouble himself with theoretical questions as to the nature of Banti's disease. If he has a patient showing the Banti pre-operative picture; if he has watched the patient long enough and studied him carefully enough to exclude leukemia, hemolytic jaundice, polycythemia and certain other conditions; if ordinary surgical considerations favor splenectomy; he need not hesitate to operate because he believes that the patient has alcoholic cirrhosis or some other equally definite cause of portal obstruction.

Case Abstracts. *Ages* are recorded as of the date of splenectomy or, if not operated upon, as of the first blood-examination recorded. *Blood:* "before operation" signifies the last examination preceding splenectomy and any preparatory transfusions; "after operation" signifies the maximum reached while under observation; the figures separated by dashes refer to hemoglobin per cent—red corpuscles—leukocytes. The *classification* of each case is indicated by italics.

CASE 1.—F. C., male, age 44. Ill with chills in Italy at about age 5. Admitted for pneumonia. Liver 3 cm. below ribs; spleen to umbilicus; mild ascites. Blood, 93—4,472,000—3000. No operation. *Etiology unknown.*

CASE 2.—F. D., male, age 27. Repeated epistaxis 1 year, distention of abdomen and hematuria 6 weeks. Marked ascites, superficial veins of abdomen distended; spleen enormous, reaching into pelvis; liver not palpable. Blood, 31—1,808,000—1850, later leukocyte counts 1600 to 3400; at times a few myelocytes. No operation. *Etiology unknown.*

CASE 3.—W. G., male, age 25. Mildly alcoholic. Penile sore at 23, no secondaries. For 6 months debility, pallor and gastric distress. Severe hematemesis 6 months and again 3 days before admission. On entrance no ascites; spleen 9 cm. below ribs; liver normal. Afterward had 2 more hemorrhages and became ascitic. Blood, 32—1,982,000—2900, platelets apparently decreased. After leaving hospital he continued to require tapping and died in 5 months. No operation, no autopsy. *Etiology unknown.*

CASE 4.—E. K., female, age 27. Metrorrhagia from puberty to age 25, no other hemorrhages; mass in upper abdomen for 6 years. Spleen occupies entire left abdomen, extending into pelvis and beyond midline; liver not felt; no ascites. Blood, 67—3,200,000—3800; platelets moderately decreased. Owing to the enormous size of the spleen and the patient's poor general condition operation was deferred. She did not apply for readmission. *Etiology unknown.*

CASE 5.—M. M., female, age 66. Abdomen increasing in size for 2 months; hematemesis 3 days before admission. Marked ascites and moderate edema; heart absolutely irregular, systolic and doubtful diastolic murmurs; spleen 4 cm. below ribs. Blood, 20—1,500,000—24,400. The patient was moribund and died before she could be transfused. No autopsy. *Etiology unknown.*

CASE 6.—S. N., male, age 13. For 5 months intermittent periods of fever, with increasing pallor. Heart normal; few râles both bases; liver palpable; spleen 4 cm. below ribs. Blood, 33—2,436,000—1300; platelets slightly decreased. No operation. No autopsy. *Etiology unknown.*

CASE 7.—W. R., male, age 18. Admitted because of recent hematemesis and tarry stools. Spleen 6 cm. below ribs; liver not felt; no ascites. Blood, 27—1,600,000—5600, later 4000; platelets decreased. No operation. *Etiology unknown.*

CASE 8.—M. S., female, age 54. Subject to epistaxis for 30 years, recently vomited a little blood; always more or less pallor, dyspnea and edema. Spleen from ribs to pelvis; liver not enlarged; no ascites, some edema. Blood, 64—3,888,000—1400; platelets much decreased, bleeding time prolonged. Owing to the immense size of the spleen and patient's poor condition she was considered inoperable. Severe hematemesis after 1 month, 9 months later became ascitic and edematous and died. No autopsy. *Etiology unknown.*

CASE 9.—S. W., female, age 20. Patient's father died after splenectomy; his spleen showed lymphoblastoma. Pallor since age 10, recent retropharyngeal abscess; admitted shortly after severe hematemesis. Spleen to umbilicus; liver normal; no ascites; no enlarged lymph nodes. Blood, 62—3,360,000—2900; platelets decreased. Splenectomy refused. Re-admitted after 6 months for hematemesis. Blood, 56—2,810,000—2950; platelets normal. Splenectomy again declined. Marrow puncture at

another hospital showed suspicion of leukemia, but patient's condition remains unchanged 2 years later. *Etiology unknown.*

CASE 10.—A. W., male, age 35. Since 25 or 30 has had gastric symptoms and has noticed tumor in left abdomen. Spleen varies in size, sometimes to pelvis. Blood, 65—4,516,000—5600; rare myelocytes. One year later, 70—3,072,000—1900; eosinophils 10.5%, rare myelocytes and numerous erythroblasts. This patient was observed for over 2 years, during which time the anemia deepened, the leukocytes varying up to 21,600; many erythroblasts and rare myelocytes (highest, 1.6%). He finally became ascitic and splenectomy was advised, but refused. *Etiology unknown.*

CASE 11.—C. B., Chinese male, age 42. Edema and abdominal distention 2 weeks. Spleen 7 cm. below ribs; liver normal; ascites. Blood, 93—6,000,000—4000; eosinophils 18%; obvious thrombocytopenia. Stool, slight amount of occult blood, no parasites. Splenectomy: condition of liver not noted; dense adhesions about spleen. Blood, after operation, 58—3,500,000—7400; platelets 72,000. Greatly improved, no return of ascites. Spleen 1050 gm., fibrotic, no leishmania. *Etiology unknown.*

CASE 12.—A. B., female, age 17. Pain in left abdomen and dysuria since minor injury 17 days before admission. Spleen to umbilicus, somewhat tender; liver normal; no ascites. Blood, 79—3,610,000—2950; platelets decreased. Pyuria. Splenectomy: spleen surrounded by dense adhesions and removed with difficulty; condition of liver not noted. Spleen fibrotic. Patient perfectly well at last note. *Etiology unknown.*

CASE 13.—E. B., male, age 17. Jaundice and anemia at age 11, followed by periods of dyspnea and pain. First seen at 14, when the spleen was 5 cm. below ribs and blood 60—3,244,000—6100; under arsenic blood improved to 76—4,152,000—6200; the spleen remaining unchanged. During 3 following years anemia slowly increased with wide fluctuations, spleen enlarged to 9 cm. below ribs; marked development of breasts and other feminine characteristics. Blood before operation 69—3,160,000—9900. Splenectomy. Marked improvement; blood in 2 months 116—5,080,000—11,600. Died of acute appendicitis $4\frac{1}{2}$ months after operation. Autopsy showed general peritonitis and bronchopneumonia; liver 1425 gm., microscopically normal; marrow from central portion of shaft of femur red, many erythroblasts, apparently hyperplasia of secondary anemia. Spleen 870 gm., fibrotic, blood sinuses distinctly outlined, lymphoid nodules small and scattered. *Etiology unknown.*

CASE 14.—C. C., male, age 12. No hemorrhages. Spleen to umbilicus; liver not palpable; no ascites. Blood during 2 years preceding operation, 60 to 85—3,260,000 to 4,880,000—4600 to 8400 (once 17,600); fragility normal. Splenectomy; liver appeared normal. Spleen showed marked fibrosis. Greatly improved, "a happy and normal child" for 2 years; then died of appendicitis. *Etiology unknown.*

CASE 15.—A. L., alcoholic male, age 46. Appendectomy at 36, hematemeses during convalescence; since then repeated attacks of severe epigastric pain. Skin pigmented, possibly slight jaundice; spleen 7 cm. below ribs; liver to umbilicus; no ascites. Blood, 77—3,470,000—7000. Died 3 days after splenectomy. Autopsy showed peritonitis; spleen fibrotic and pigmented; liver, *cirrhosis* of *alcoholic* type, also some nodules suggestive of toxic cirrhosis.

CASE 16.—A. M., alcoholic male, age 58. Gastric distress and vomiting 3 years, occasional tarry stools and recent ascites (tapped). Skin pigmented; auricular fibrillation; spleen easily felt; ascites. Blood, 70—3,140,000—4800; later leukocytes varied from 2000 to 4000. Abdomen tapped several times. Patient was considered too ill for splenectomy and left hospital against advice. Readmitted, 3 weeks later, moribund. Autopsy: spleen 520 gm., congested and somewhat fibrotic; liver 890 gm.,

gross appearance suggested toxic cirrhosis, but microscopic examination showed *alcoholic cirrhosis* and hemochromatosis.

CASE 17.—H. W., alcoholic male, age 53. Dyspnea and edema 13 years; tapped for "pleurisy" 8 years ago, at which time he was told that the liver was large; jaundiced at times for 6 years. Marked jaundice; large heart with loud systolic murmur; emphysema; slight ascites; neither liver nor spleen felt. Blood, 45—3,300,000—10,000, later counts showed moderate leukopenia. Developed dullness at right base with cough and purulent expectoration. Died after severe hemorrhage, thought to be from stomach. Autopsy: small empyema at right base communicating with a bronchus, mitral and aortic valves thickened and calcified; spleen 535 gm., fibrotic; liver showed typical *alcoholic cirrhosis*.

CASE 18.—D. B., alcoholic male, age 50. Admitted for hernia. Spleen 5 cm. below ribs; liver barely felt; slight jaundice; marked ascites. Blood, 70—3,180,000—4000. Splenectomy; liver small and embedded in dense adhesions, preventing palpation. After operation blood 96—4,500,000—12,600. Patient continued to require aspiration at frequent intervals. Spleen fibrotic. *Alcoholic cirrhosis*.

CASE 19.—M. J., mildly alcoholic female, age 40. Malaria at 30; pelvic(?) operation at 33, at which time large spleen was discovered. Since then periods of abdominal distention, no hemorrhages. Progressive distention for 2 months. Moderately emaciated; marked ascites; spleen below umbilicus; liver normal. Blood, 20—1,664,000—1500; platelets decreased. Abdomen tapped twice; transfused 900 cc. Splenectomy; liver small and "hobnailed;" many adhesions. Died in 24 hours. Spleen 1025 gm., markedly congested, somewhat fibrotic. No autopsy. *Alcoholic cirrhosis*.

CASE 20.—C. K., female, age 38. Three hemorrhages from stomach in 10 months; abdomen enlarged 5 months, finally aspirated. Ascites; spleen to crest of ilium; liver not felt. Blood, 43—2,840,000—750; platelets much decreased. Splenectomy: liver large and finely irregular; spleen 23 by 15 by 5 cm., fibrotic. Much improved for a month, then after exposure to scarlet fever temperature rose to 104° F., after which chills, sweats and septic fever continued up to death 4 months from operation, apparently septic endocarditis. *Alcoholic cirrhosis*.

CASE 21.—M. W., probably alcoholic female, age 57. Repeated hematemesis and constant "stomach trouble" for 30 years. Spleen 4 cm. below ribs; liver just palpable; no ascites. Blood, 30—2,136,000—1650; slight decrease in platelets. Splenectomy: liver small and hard; slight ascites; stomach rigidly constricted (hour-glass); gall stones. Spleen fibrotic. Much improved, but continued to have occasional hemorrhages. Died of cerebral hemorrhage at 64. *Alcoholic cirrhosis*.

CASE 22.—M. M., alcoholic, female, age 53. For 4 weeks epigastric pain, hematemesis and tarry stools. Spleen 4 cm. below ribs; liver not palpable; slight ascites. Blood, 43—3,000,000—2200. *Alcoholic cirrhosis*.

CASE 23.—W. Z., alcoholic male, age 40. Hematemesis day before admission, repeated several times later with tarry stools. Ascites tapped. Loud systolic murmur at apex and aortic area; spleen 4 cm. below ribs; liver not palpable. Blood, 70—4,100,000—3800; platelets greatly decreased. No operation. *Alcoholic cirrhosis*.

CASE 24.—T. C., female, age 51. Epistaxis, but no hemorrhage from alimentary tract; jaundice 6 weeks. Spleen 6 cm. below ribs; liver not palpable; slight ascites. Blood, 60—3,620,000—2600; platelets decreased. Splenectomy: liver much contracted and coarsely lobulated. Died on table from arterial hemorrhage. Spleen, 400 gm., fibrotic and congested. Liver: a small piece removed at operation showed *toxic cirrhosis* microscopically. No autopsy.

CASE 25.—R. J., male, age 14. Ill 4 years in Cuba; following a febrile attack remained pale and weak. Chronic diarrhea, 6 to 14 daily stools, containing blood. Emaciated; spleen 10 cm. below ribs; liver not palpable. Blood, 26—2,261,000—4200; platelets moderately decreased. Splenectomy, death. Autopsy: ulcerative colitis involving entire colon and lower 40 cm. of ileum; spleen 780 gm., pulp greatly increased, great number of small, moderately distended sinuses, some fibrosis; liver 1200 gm., surface irregular and coarsely nodular, on section it presents very irregular islands of liver separated by connective tissue, microscopically it is typical *healed acute yellow atrophy*.

CASE 26.—E. S., female, age 16. For 5 months occasional edema and slight jaundice, urine constantly containing bile. Admitted with acute otitis media and later operated for mastoiditis, of which she died. Blood, 74—4,760,000—9100. Autopsy: spleen 620 gm., fibrotic; liver 670 gm., rough and nodular, microscopically *healed acute yellow atrophy*.

CASE 27.—M. D., alcoholic female, age 36. Epigastric distress after meals 15 years; hematemesis twice in 9 months; abdominal swelling 3 weeks. Neither liver nor spleen palpable because of ascites, which required frequent aspiration. Wassermann positive, but no improvement followed prolonged arsphenamin treatment. Blood, 40—2,240,000—4200; platelets slightly decreased. Splenectomy: liver greatly atrophied, its surface irregular, many adhesions; spleen high and adherent, 335 gm., fibrotic and congested, vessels sclerotic, Malpighian corpuscles not grossly visible. Blood, after operation and 3 transfusions, 81—4,650,000—6800; 4 months later, 75—3,910,000. Continued to require tapping about every 2 weeks, died of hematemesis 16 months after operation. Autopsy: peritoneum thickened, with massive adhesions everywhere; esophageal varices, probably site of recent hemorrhage; liver 1080 gm., capsule and portal connective tissue thickened so that islands of liver tissue are marked off, dense scars in places; single gall stone. Microscopically the liver shows large fibrous scars infiltrated with lymphocytes, no bile-duct proliferation. *Infectious cirrhosis*, presumably *syphilitic*.

CASE 28.—D. D., male, age 57. Syphilis at 17, Wassermann negative for past 4 years. Increasing pallor 3 years, recent dysuria and loss of weight. Yellowish pallor; liver 3½ cm. below ribs; spleen 6 cm. below umbilicus. Blood, 43—2,557,000—8200—normoblasts and megaloblasts—platelets normal—reticulocytes 4.2%; volume index 0.67; hemolysis in NaCl solutions begins at 0.525 and ends at 0.375%. Later leukocyte counts 3200 to 4300. Under radiation the spleen became smaller and general condition better. Refused splenectomy and died. No autopsy. Probably *syphilitic cirrhosis*, possibly hemolytic jaundice.

CASE 29.—S. G., syphilitic female, age 42. For 3 months pain in left upper abdomen and continuous flowing; lost 30 lbs. in 5 months. General condition poor; spleen 6 cm. below ribs, tender; liver not enlarged; ascites. Blood, 45—2,680,000—1850—Wassermann positive. Cancer of uterine cervix. Splenectomy: inoperable cancer of pelvis found at operation. Died, no autopsy. Spleen 1715 gm., fibrotic. Classed as *syphilitic cirrhosis*.

CASE 30.—J. P., alcoholic male, age 45. Nosebleeds for 6 months, dyspnea 10 months; jaundice 4 months ago. Marked emphysema; spleen 8 cm. below ribs; liver not enlarged; moderate ascites; edema of feet. Blood, 45—3,500,000—2800; platelets appear decreased; Wassermann positive. Before operation, 46—3,200,000—7600. Transfused, and splenectomy done; died. Autopsy: esophageal varices with minute rupture; melena; acute general peritonitis; S. hemolyticus in blood; aorta suggestive of syphilis; spleen 855 gm., fibrotic; liver 1380 gm., irregular (*hepar lobatum*) and other changes of *syphilitic cirrhosis*; splenic vein dilated to 1 cm.

CASE 31.—A. W., female, age 46. For 3 months bloody stools and pain in left abdomen. Spleen palpable. Blood, 48—3,000,000—4000; Wassermann positive. Under treatment with arsphenamin the blood improved and the spleen diminished in size. *Syphilitic cirrhosis*.

CASE 32.—G. C., female, age 65. At age 56 exploratory laparotomy was done, diagnosis splenic anemia, spleen not removed. Ill for 3 months, nausea, epigastric pain, hematemesis and swelling of abdomen and extremities. Spleen barely palpable; liver 7 cm. below ribs; ascites; slight jaundice; auricular fibrillation. Blood, 85—4,500,000—6250. Died of hematemesis. Autopsy: spleen large, showing microscopically congestion and fibrosis; liver small and cirrhotic, its appearance suggestive of toxic cirrhosis, but after examining microscopic sections the pathologist (F. B. Mallory), is unwilling to classify it; thrombosis of splenic and portal veins. *Unclassified cirrhosis*.

CASE 33.—R. F., alcoholic female, age 45. Abdominal distention 4 weeks. Spleen 6 cm. below ribs; moderate ascites. Blood, 84—4,900,000—4400, later 72—3,500,000. Died of hematemesis. Autopsy: spleen 1000 gm., fibrotic with marked distention of bloodvessels; liver 1380 gm., cirrhotic, marked cellular hyperplasia about vessels, some of which are completely obliterated; possibly syphilitic; portal and splenic veins sclerosed; ulcerative colitis. Classified as *atypical cirrhosis*.

CASE 34.—L. H., male, age 19. Pallor 1 year; abdomen swollen 1 week; diarrhea. Spleen 3 cm. below ribs; liver normal. Blood, 77—4,190,000—3550; platelets much decreased. Splenectomy: liver small and soft, with a "wavy" upper surface. Patient did not improve and died 2 months later of acute nephritis. Spleen fibrotic. *Cirrhosis of undetermined type*.

CASE 35.—A. K., female, age 25. Five months before admission vomited blood and a few days later aborted. Ascites tapped 3 times. Three months before admission operated for retroperitoneal abscess (right), followed by weekly tapings. Emaciated; marked ascites prevented palpation of abdominal organs. Blood, 36—4,110,000—7500; platelets decreased. Transfusion and splenectomy: many small mesenteric cysts; liver very small and hard, *type of cirrhosis not determined*. Required aspiration twice after operation; blood rose to 56—4,270,000—10,700. After 4 years patient is in excellent condition and ascites has not recurred. Spleen 420 gm., very marked fibrosis.

CASE 36.—M. A. L., female, age 45. At 34 had edema and ascites for 1 month, spleen and liver were large, heart markedly enlarged, with loud systolic murmur. Diagnosed splenic anemia. Blood, 45—2,726,000—3000; Wassermann negative. At 38 liver was palpable, spleen to umbilicus. Blood, 25—1,640,000—2400. Readmitted at 44; spleen 12 cm., liver 3 cm. below ribs; edge irregular and rough; marked ascites; blood, 19—1,390,000—1600. Refused splenectomy, died 5 months later. Autopsy: spleen 1350 gm., fibrotic, some phagocytosis; splenic vein patent; liver 1650 gm., *portal cirrhosis of undetermined type*; heart 400 gm., valves normal.

CASE 37.—I. N., female, age 53. Indefinite debility 10 years; diarrhea and abdominal cramps 6 weeks; mildly jaundiced at times. Spleen to umbilicus; liver 5 cm. below ribs. Blood, 39—3,480,000—2900; platelets reduced; hemolysis in NaCl solutions begins at 0.525, ends at 0.3%. Splenectomy: liver somewhat rough and appeared cirrhotic. Marked improvement in blood and general condition. Still well after 6 years. Spleen 705 gm., dilated sinuses and fibrosis. A bit of liver removed at operation showed slight *cirrhosis of undetermined type*.

CASE 38.—I. W., female, age 26. Double salpingectomy at 23, followed by persistent menorrhagia. Very pale; spleen 2 cm., later 5 cm., below ribs; liver not felt; no ascites. Blood, 18—2,190,000—3000. Several transfusions and splenectomy: liver small and scarred, possibly toxic cirrhosis.

Spleen fibrotic. Marked improvement. Menorrhagia continued for 2 years, when she was readmitted with blood 44—4,970,000—12,000. Transfusion and hysterectomy, followed by marked improvement in blood and general condition. *Cirrhosis of undetermined type.*

CASE 39.—P. B., male, age 18. Admitted in an acute respiratory infection. Spleen 5 cm. below umbilicus; liver 6 cm. below ribs. No ascites. Blood, 60—3,542,000—4900; platelets normal. No operation. *Classed as non-cirrhotic liver disease.*

CASE 40.—B. B., female, age 36. A sister and a niece have had splenectomies for causes unknown. Frequent gastric upsets with jaundice since a "grip" infection 4 years ago. No jaundice at present; liver slightly enlarged; spleen to umbilicus. Blood, 61—3,212,000—9500; icterus index 12; platelets normal; hemolysis in NaCl solutions normal; stool contains occult blood. Splenectomy: liver slightly enlarged. Spleen markedly fibrotic. After 9 months hemoglobin was 85 and patient's condition good. *Classed as non-cirrhotic liver disease.*

CASE 41.—N. B., female, age 27. Appendectomy at 21, drained; operation followed by sepsis, relieved after a month by evacuation of an abscess "behind the liver." Operation at 25 for ventral hernia, dense adhesions found. Sixteen months later vomited blood and had tarry stools. Spleen 5 cm. below ribs, transversely located; liver not felt; no ascites. Blood, 75—3,500,000—3250; platelets appear decreased. Splenectomy and transfusion (750 cc.); liver very small, both it and spleen embedded in dense adhesions. Blood slowly improved to 80—4,000,000—11,630; platelets 256,000. General condition greatly improved. Spleen 680 gm., fibrotic, hemorrhages into trabeculae, perisplenitis.

CASE 42.—E. D., male, age 12. Appendectomy at 6; a year later severe hematemesis and ascites (aspirated); hematemesis again at 11. Spleen 4½ cm. below ribs; liver barely palpable. Blood 35—3,700,000—4000; fragility normal. Later leukocytes 4400 to 7150. Splenectomy: liver normal, dense adhesions about spleen, which was adherent to stomach. Spleen 525 gm., fibrotic, several small infarcts. Marked improvement; final blood 90—5,010,000—14,850.

CASE 43.—M. H., female, age 40. Six operations since age 21, including appendicitis, gastric ulcer and ovarian cyst; repeated epistaxis for 18 months; several hemorrhages from stomach. Spleen easily felt; liver normal. Blood, 43—3,700,000—14,400; leukopenia never observed; hemolysis in NaCl solutions begins at 0.450, complete at 0.250%. Splenectomy: liver small, many firm adhesions about both liver and spleen interfered with satisfactory exploration. Died 2 days later; no autopsy. Spleen 250 gm., markedly fibrotic.

CASE 44.—C. M., female, age 51. Appendectomy at 45, appendix gangrenous with a walled-off abscess and many adhesions. Emphysema; spleen 8 cm. below ribs; liver not felt; ascites. Blood, 32—3,360,000—5300, later leukocyte counts 2000 to 9800; Wassermann test positive. Readmitted at 59 with acute intestinal obstruction; operation and death from general peritonitis. Autopsy: gall bladder buried in old adhesions, which extend to surrounding viscera; spleen 880 gm., fibrotic; liver 1600 gm., microscopically normal; mesenteric vessels thrombosed, with infarction of gut.

CASE 45.—H. D., not alcoholic, male, age 30. Appendectomy at 20; gastro-enterostomy at 26; hematemesis 6 months ago; pallor 5 years. Spleen 3½ cm. below ribs; liver normal; slight ascites. Blood, 26—2,478,000—3000; platelets decreased. *Adhesions.*

CASE 46.—M. M., male, age 46. Known for years as a case of *congenital heart disease*. Recent hematemesis; loud systolic murmur and thrill; spleen to umbilicus; liver not felt; slight edema of feet and ascites. Blood, 53—3,590,000—4050, later 2600. Before operation, 70—3,750,000—4700;

platelets moderately decreased. Splenectomy: liver slightly enlarged, smooth and normal in consistency. Blood after operation, 98—5,000,000—10,650; platelets normal. Much improved and returned to laborious work. Spleen: blood sinuses well defined, walls thickened and consist of collagen reticulum in the meshes of which are numerous leukocytes and plasma cells; sinuses contain polymorphonuclears, lymphocytes and endothelial leukocytes, a number of which are phagocytic and contain lymphocytes and red corpuscles.

CASE 47.—R. C., female, age 30. Tumor in left abdomen 3 years. Its nature was not suspected till exploratory operation showed it to be a greatly *ptosed spleen*, which was removed. Blood, after operation, 75—5,680,000—13,800. Later, hemoglobin 95, leukocytes 10,600, eosinophils 25%. Spleen 470 gm., fibrotic, sinuses very distinct and dilated. Followed 20 months, during which time she remained well.

Summary. On the basis of a study of 47 cases the view is expressed that in the majority of patients presenting the clinical picture of Banti's disease (splenomegaly with fibrosis, microcytic anemia with leukopenia and a late stage with hemorrhages and ascites) the condition is dependent upon various intra-abdominal lesions obstructing the venous outflow of the spleen. By far the commonest of these is liver cirrhosis of various types. As Banti has limited the definition of the disease which bears his name in such a manner as to exclude these cases it is thought best to segregate them under a distinctive name. However, splenectomy is indicated just as in Banti's disease, regardless of the nature of the underlying lesion.

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THE DISTINCTION BETWEEN SPLENIC ANEMIA AND SUB-LEUKEMIC SPLENIC RETICULO-ENDOTHELIOSIS.*

By HERBERT Z. GIFFIN, B.S., M.D., F.A.C.P.,

HEAD OF SECTION IN DIVISION OF MEDICINE; PROFESSOR OF MEDICINE,

AND

CHARLES H. WATKINS, B.A., M.A., PH.D., B.S., M.B., M.D.,

ASSOCIATE IN SECTION IN DIVISION OF MEDICINE; ASSISTANT PROFESSOR OF MEDICINE,
ROCHESTER, MINN.

(From The Mayo Clinic and The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota.)

NOT many decades ago, and within the memory of living physicians, cases of primary splenomegaly were classified as cases of leukemia, chronic malaria, or splenic anemia. Gradually, however, physicians have learned to recognize clinically as separate syndromes certain diseases simulating splenic anemia. The features characterizing these syndromes were clarified and simplified, and it became possible to diagnose clinically hemolytic icterus, syphilitic splenomegaly, chronic septic splenomegaly and, in a certain proportion of instances, Gaucher's disease, primary sarcoma of the spleen and subleukemic forms of leukemia. Now it is probable that it will be possible to divorce still another condition from the group of cases of splenic anemia and, if so, to save the patient the ill-advised ordeal of splenectomy. We refer to subleukemic splenic reticulo-endotheliosis, which at the time of examination is either an aleukemic or, more accurately, a subleukemic form of monocytic leukemia associated with splenomegaly as a prominent clinical feature.

The extent and importance of the reticulo-endothelial system is not generally appreciated; knowledge concerning its physiology and pathology is complicated and confusing. It is probable, however, that the studies of hematologists and tissue morphologists will lead the way to a clearer conception of clinical manifestations and their relation to pathologic findings. Special methods of cell staining and study, by trained observers, are necessary to the proper interpretation of both hematologic and pathologic data.

Active cells of the reticulo-endothelial system, both as histiocytes of the tissues and as syncytial cells of sinusoids, perform amazing functions in hemopoiesis, hemolysis, phagocytosis, storage of colloids and pigments, elaboration of substances to be passed on to other cells, metabolism of fats, lipoids, iron and hemoglobin, and in defense reactions of the body. Therefore, any clinical evidence of disorder of the reticulo-endothelial system must be regarded

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as an indication of profound organic and functional disturbance of the organism. The histiocyte of the reticulo-endothelial system is a partially differentiated cell and probably cannot, under normal conditions, act as parent cell of either lymphocyte or granulocyte. There is reason to believe, however, that under certain conditions the histiocyte may be the parent cell of the monocyte, although monocytes are usually derived from myeloblasts. Surely, if leukemic reticulo-endotheliosis and monocytic leukemia are not one and the same disease, they are closely akin.

In cases of leukemic reticulo-endotheliosis the primitive free reticulo-endothelial cell may be found in the blood in addition to the reticular type of monocyte. This primitive cell is generally larger than the leukocyte and usually has an eccentric nucleus, which is frequently elongated but may be rounded or indented. The nuclear membrane is clearcut, sharp and smooth, and one or two nucleoli may be present; the chromatin is blue with Wright's stain, sharply differentiated and arranged in fine granular strands. The cytoplasm is grayish-blue in contrast to that of the lymphocyte and blotchy or granular in appearance; cytoplasmic protrusions are common. The entire cell is youthful and delicate in appearance. Recognition of this cell in blood smears is a most important element in diagnosis.

Clinically, reticulo-endotheliosis may be manifest in three characters: (1) As storage or lipoid histiocytosis, of which Gaucher's disease, Niemann-Pick's disease and the Hand-Schüller-Christian syndrome are examples; (2) as infectious hyperplastic reticulosis, as in certain recurrent infections and sepsis, in infectious monocyctosis, and in occasional cases of bacterial endocarditis; (3) as leukemic reticulo-endotheliosis.

Patients with leukemic reticulo-endotheliosis may present themselves with generalized involvement of the entire reticulo-endothelial system, with or without localized tumors, with predominant involvement of the bone marrow, predominant involvement of lymphatic structures, or predominant involvement of the liver or of the spleen. Any of these forms may be frankly leukemic (monocytic), sub-leukemic, or aleukemic. Leukemic splenic reticulosis is not difficult of recognition because of the high percentage of reticular monocytes in the blood; diagnosis of aleukemic forms may be clinically impossible. It is of the subleukemic type of splenic reticulo-endotheliosis that we wish to report 2 instances in which the diagnosis could have been made at an earlier date.

Case Abstracts. CASE 1.—A man, aged 33, had always been in good health until the present illness. During the preceding 5 years he had noticed some fatigability and slight loss of weight. During the preceding 3 years he had had 4 episodes like influenza associated with a vesicular eruption, chiefly of the wrists, elbows and knees. Splenomegaly had been noted only 2 weeks preceding examination, and weakness recently had

become more marked than before. The patient was only 5 feet 3 inches (160 cm.) tall, and weighed 106 pounds (48.1 kg.); his normal weight had been 115 pounds (52.1 kg.).

General physical examination, May 5, 1930, revealed nothing of apparent significance aside from very slight enlargement of the liver and considerable enlargement of the spleen. The spleen extended almost to the median line, and to the level of the umbilicus. The blood showed: hemoglobin, 12.7 gm. per 100 cc.; erythrocytes, 3,590,000 and leukocytes, 2600 per c.mm.; lymphocytes, 70.5%; monocytes, 1.5; neutrophils, 27; eosinophils, 0.5. (Subsequent study of blood smears led to the recognition of an occasional reticular cell.) One count of platelets, by the direct method, was 134,000 per c.mm., but platelets were very scarce in the smears. Bleeding time was 1.5 minutes and clot retraction was only slight at the end of 23 hours. The fragility test showed slight increase in resistance of erythrocytes. Urinalysis, serologic test of the blood, and roentgenologic examination of the thorax gave negative results. Liver function test showed no retention of dye; the value for serum bilirubin was 1.1 mg. per 100 cc. In spite of the delayed retractility of the clot and reduction in the number of platelets there had been no spontaneous hemorrhagic manifestations.

Splenic anemia was thought to be the most likely diagnosis, and splenectomy was performed May 28, 1930. The spleen was markedly enlarged, weighing 1050 gm.; there were few perisplenic adhesions. The liver seemed to be normal on palpation, and there was no enlargement of bloodvessels around the stomach.

The patient returned December 16, 1930. He was considerably better and had gained 9 pounds (4.1 kg.), but still felt exhausted. The blood showed 15.7 gm. of hemoglobin; 3,970,000 erythrocytes and 5200 leukocytes; lymphocytes, 61.5%; monocytes, 1.5; neutrophils, 36; eosinophils, 0.5; basophils, 0.5; reticulocytes, 0.5. Study of the smears disclosed definite macrocytosis, lymphocytosis and toxicated neutrophils; reticular cells were not recognized. Liver function test revealed no retention of dye; the value for serum bilirubin was 1.5 mg. per 100 cc.

The patient was next seen June 21, 1933, about 3 years following splenectomy. His condition had become very much worse during the preceding month, the complaints being chiefly of weakness, chilliness and anemia. His weight was not reduced; it was 110 pounds (49.9 kg.). He was pale and sallow, but not jaundiced. Superficial lymph nodes were not noticeably enlarged, although a few were barely palpable. The liver, however, had become definitely larger and extended three fingers' breadth below the costal arch. Liver function test, however, gave no evidence of retention of dye; the value for serum bilirubin was 1 mg. per 100 cc. There was some abdominal distention, slightly suggestive of retroperitoneal involvement. The blood showed: hemoglobin, 10 gm.; erythrocytes, 3,630,000; leukocytes, 8200; lymphocytes, 90.5%; monocytes, 2; neutrophils, 6.5; eosinophils, 1; reticulocytes, 0.3. Study of the smears disclosed no definite immaturity, aside from the presence of a few cells which were regarded as reticular in origin.

The patient was last under observation in December, 1933, 3½ years after splenectomy. December 9, 1933, the blood showed 7.6 gm. of hemoglobin; 1,520,000 erythrocytes and 6100 leukocytes; lymphocytes, 64.5%; neutrophils, 8.5; eosinophils, 1; reticulo-endothelial cells and reticular monocytes, 26. This high percentage of reticular cells led to a review of all former available blood smears, with the result that after prolonged study an occasional reticular cell could be found and reticular monocytes were not infrequently observed.

Treatment, which included transfusions and the use of Roentgen rays, effected no definite improvement and the patient was advised to return to

his home. When he last was heard from, in April, 1934, he was weak, anemic and in very poor health.

The spleen was examined by Dr. W. C. MacCarty, who reported: "The spleen weighs 1050 gm., is normally shaped and somewhat pale. Its density is slightly increased. The cut surface is smooth, red and fairly homogeneous in texture. Microscopically, the appearance of the organ simulates that of splenic anemia; however, there is in certain areas an increase in large ovoidal and spheroidal cells, apparently either of fibroblastic or reticulo-blastic origin. The organ is congested and contains some intra-cellular and extra-cellular pigment. The Malpighian corpuscles are almost invisible, as are their germinal centers."

Dr. Hal Downey also examined sections. His report was as follows: "Microscopically, the spleen shows areas of hyperplasia of the reticulo-endothelium; there is not a uniform hyperplasia, however. Some small areas are very hyperplastic and seem to give rise to large, pale monocytoïd cells. Much of the pulp seems to be fairly normal except for the occasional presence of these cells and the absence of lymphocytes. In a few places, reticular cells can be seen to form large plasmodia, which connect with the surrounding reticulum. A very few small follicles with germinal centers can be found. Lymphocytes are scarce. The splenic tissue indicates a diagnosis of leukemic reticulo-endotheliosis in the early stages" (Fig. 1).

CASE 2.—A man, aged 50, for 10 months had had pain in the right leg, weakness and lassitude; and diagnoses of sciatica and neuritis had been made. In the course of the preceding 6 months a slight hemorrhagic tendency had developed, evidenced mostly by bleeding on shaving; there had been no gross hemorrhages. The patient had lost about 10 pounds (4.5 kg.); splenic enlargement had not been noted.

Physical examination, October 13, 1930, gave evidence of slight enlargement of the liver, and definite, although moderate, enlargement of the spleen. The blood showed: hemoglobin, 11.4 gm.; erythrocytes, 2,910,000; leukocytes, 2000; lymphocytes, 54%; monocytes, 2.5; neutrophils, 40; eosinophils, 3.5; reticulocytes, 0.9; platelets, 64,000 per c.mm. Bleeding time was 4.5 minutes; coagulation time of the venous blood, 10 minutes; calcium time, 9.5 minutes; prothrombin time, slightly prolonged, and retractility of clot was not present in 6 hours. Examination of blood smears gave no evidence of immaturity of cells; there was a slight tendency to macrocytosis, but no shift to the right of the polymorphonuclears. (Subsequent study of blood smears led to the recognition of 2% of reticular cells.) Serologic tests of the blood gave negative results. Roentgenologic examination of the right hip gave evidence of chronic destructive arthritis. A marked degree of prostatitis was demonstrated. On liver function test, no evidence of retention of dye was obtained.

After several days' consideration of the case the condition was, with some misgivings, classified as splenic anemia with secondary purpuric manifestations similar to those found in hemorrhagic purpura. Splenectomy was performed October 25, 1930. Adhesions about the spleen were few. There was no excess dilatation of veins, either in the splenic pedicle or around the stomach. The liver and gall bladder seemed to be normal.

Convalescence was satisfactory, and the patient was dismissed from hospital on the 14th day, at which time the value for hemoglobin was 57%; erythrocytes numbered 3,490,000; leukocytes, 4600 and platelets 440,000 per c.mm. of blood; clot retraction was satisfactory in 1 hour.

The patient returned for reexamination 8 months later, July 27, 1931, stating that he had been very much improved until May, 1931, when he had begun to notice weakness and anemia. There had been no gross bleeding. The leukocyte count was said to have been very low, and at times the percentage of neutrophils was very low. The edge of the liver was



FIG. 1.—(Case 1.) Splenic tissue. Hyperplastic reticulum with reticular monocytes.

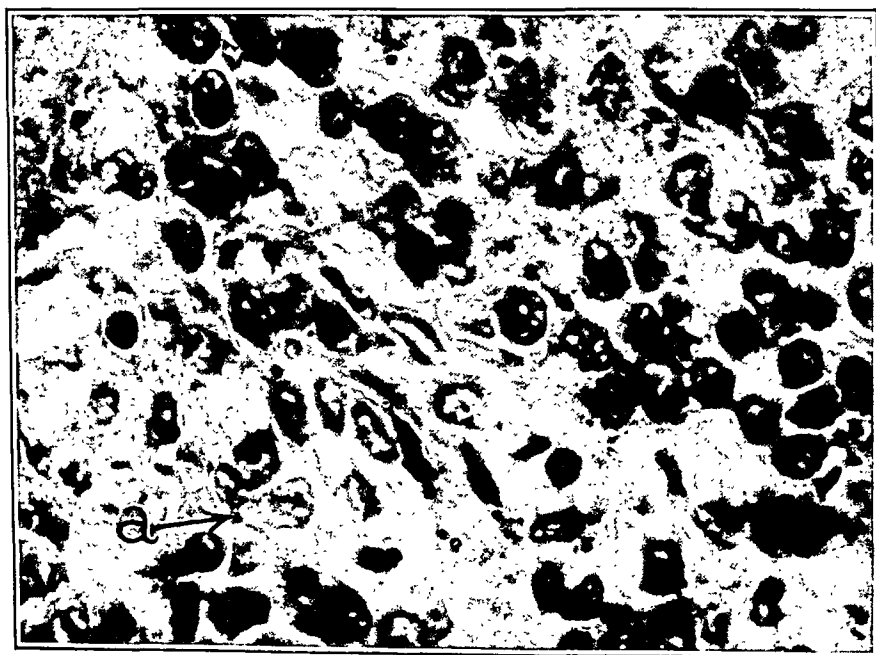


FIG. 2.—(Case 2.) Splenic tissue. Hyperplastic reticulum, with formation of reticular monocytes. *a*, Reticular cell in process of extrusion into splenic sinus.

just palpable; lymph nodes were not enlarged. Examination of the blood gave the following results: hemoglobin, 26%; 1,650,000 erythrocytes and 3600 leukocytes; lymphocytes, 50%; monocytes, 1; neutrophils, 28, and reticular cells and reticular monocytes, 21; occasional normoblasts were found; the percentage of reticulocytes was 0.4. Bleeding time was 3 minutes; coagulation time of venous blood, 5 minutes; calcium time, 10.5 minutes; prothrombin time, normal, and retractility of clot was not yet present in 7 hours. Platelet counts were 70,000 and 58,000 per c.mm. Roentgen films of the lower ends of the femurs and of the upper ends of the tibiae were negative for evidence of abnormalities of bone.

Treatment was of no avail in combating the anemia and the patient was allowed to return home, where he died September 8, 1931. Necropsy was not obtained.

The spleen was examined by Dr. W. C. MacCarty, who reported: "The spleen weighs 800 gm. The density is slightly increased. The cut surface is homogeneous in texture. Microscopically, there is a generalized hyperplasia of large ovoidal and spheroidal cells, apparently of fibroblastic or reticuloblastic origin. Malpighian corpuscles are entirely obliterated. The tissues are congested and in places contain free red cells as well as pigment."

Dr. Hal Downey also examined the spleen, and his report is as follows: "This is one of the best specimens I have seen for evidence in favor of the derivation of monocytoïd leukemic cells from reticulum. The structure of the spleen is very uniform, except that in some regions the number of free erythrocytes is greater than in others, and in certain areas free monocytoïd cells are somewhat more numerous, while in other regions hyperplastic reticulum predominates. There is no nodular arrangement of leukemic cells and the follicles have disappeared.

"Monocytoïd cells are large, rather pale, and contain relatively large, pale nuclei with one or two round nucleoli. Occasionally one sees a large or medium sized lymphocyte, but it is evident that the leukemic cells are not lymphocytes. The cytoplasm is very much less basophilic than that of lymphocytes and the nuclear pattern is different. The nuclei of the monocytoïd cells are frequently indented and their cytoplasm is not as homogeneous and dense as that of lymphocytes. Normal sinuses are scarce. The connective tissue walls of the sinuses are usually thickened and some of the sinuses seem to have lost all of their syncytial cells. Two sinuses were observed in which the proliferating reticulum surrounding the sinus had broken through the wall. The nucleus of one of the reticulo-endothelial cells was within the sinus, that portion of the cytoplasm had become rounded, and a distinct pedicle extended from this rounded portion through an opening in the wall of the sinus to connect with the surrounding reticulum. Actual budding off of leukemic cells from hyperplastic reticulum can be seen in many places. In fact, the entire picture is typical of leukemic reticulo-endotheliosis of the type in which the leukemic cells of the blood are monocytoïd in character and at the same time show evidence of their origin from cells of the reticulo-endothelial system" (Fig. 2).

Comment. The literature of leukemic reticulosis will not be reviewed at this time. Cases in which this condition has been recognized have been reported in increasing numbers within recent years; the total number in the literature is approximately 40. A few of these have conformed to the syndrome considered in this paper; namely, subleukemic splenic reticulosis.

Detailed and prolonged morphologic study of the blood is necessary to establish the diagnosis. Reticular cells and reticular mono-

cytes have been described early in this paper. Their recognition in blood smears is not difficult, but finding them in the early stages of the disease requires time. One is likely to classify them as mature monocytes, and their numbers may not be great enough to alter the normal percentage of monocytes. In the later stages of the disease the morphologic diagnosis is simpler because of the presence of a much higher percentage of reticular cells and reticular monocytes; in these cases they were, respectively, 26 and 21%. In both of the cases reported, reticular cells were not found on routine examination of the blood at the first visit, but on subsequent review of these blood smears reticular cells were demonstrated.

In the cases reported, macrocytosis of moderate degree, with hypochromasia, was present. The number of platelets was slightly reduced in Case 1 and markedly reduced in Case 2. The neutrophils showed a general shift to the left, their nuclei presenting some blurring of chromatin and irregularity of outline, and their cytoplasm containing granules which were larger than normal, were more basophilic, and were more irregularly placed. These toxic changes grew more marked as the disease progressed and the anemia became more severe.

The first patient presented a reduction of platelets and a delay of clot retraction; the second patient complained of free bleeding from cuts and had a low platelet count, a prolonged bleeding time and delayed retractility of clot. Hemorrhagic features have been noted also in reported cases. Leukopenia and an absence of leukocytosis were constant in these cases, even in the terminal stage of the disease; relative lymphocytosis also was present. Preceding episodes of infection were indicated by the histories. Liver function tests, even in the more advanced stages of the disease, revealed no retention of dye. It appears, therefore, that certain clinical features were present in these 2 cases which should have made one hesitate to diagnose splenic anemia and to search more carefully for reticulo-endothelial cells in the blood.

Summary and Conclusions. Two cases originally diagnosed as splenic anemia and subsequently classified as subleukemic splenic reticulo-endotheliosis are reported; the first of these was seen in an early stage of the disease; the second was more advanced at the time of the first examination. The clinical and morphologic features which should have suggested an earlier diagnosis of splenic reticulosis are as follows: history of preceding episodes of infection; a short history of the development of splenomegaly; slight purpuric manifestations with abnormalities of coagulation; leukopenia or normal leukocyte count with relative lymphocytosis and, in prolonged study of blood smears, the presence of reticulo-endothelial cells and the reticular type of monocyte. As the cases became more definitely leukemic, a higher percentage, between 20 and 30, of reticular cells could be found, even though leukocytosis was not present. The

advanced stages in both cases were characterized by severe macrocytic anemia, which did not respond to treatment. The infectious hyperplastic type of reticulo-endotheliosis, in which reticular cells may be found in the blood smears, can be distinguished from leukemic reticulo-endotheliosis by the presence of an increased percentage of polymorphonuclears, the absence of immature reticular monocytes, and clinical manifestations of a predominating infectious process. Cases of subleukemic monocytic myelosis reveal the presence of stem cells of the myeloid series and the absence of typical reticular cells.

In splenic anemia, there is usually no definite history of episodes of infection, a history of fever is uncommon and splenomegaly usually has been present for years. Purpuric features are occasionally present in cases of splenic anemia but apparently they are not nearly so common as with reticulo-endotheliosis. In splenic anemia the test of liver function almost always gives evidence of at least a moderate, and sometimes an extreme, grade of retention of dye, and gross gastro-intestinal hemorrhage is more common. Leukopenia with lymphocytosis is not uncommon in splenic anemia, but examination of blood smears, in addition to the absence of reticular cells, usually reveals more poikilocytosis and less macrocytosis. Prolonged study of blood smears is essential to the demonstration of the presence or absence of reticular cells, particularly in the early stages of splenic reticulosis.

COMPARATIVE VALUES OF SEVERAL ANTIDOTES IN CYANID POISONING.*

BY K. K. CHEN, PH.D., M.D.,
DIRECTOR OF PHARMACOLOGIC RESEARCH,

CHARLES L. ROSE, B.S.,
PHARMACOLOGIST,

AND

G. H. A. CLOWES, PH.D., SC.D.,
DIRECTOR OF RESEARCH, THE LILLY RESEARCH LABORATORIES,
INDIANAPOLIS, IND.

(From the Lilly Research Laboratories.)

OCCUPATIONAL cyanid poisoning may occur in the hydrocyanic acid fumigation of ships and buildings. For example, the United States Public Health Service, according to Surgeon General Cum-

* Read in part before the American Public Health Association at Indianapolis, October 10, 1933; the Indianapolis Medical Society, February 13, 1934; and the American Society for Pharmacology and Experimental Therapeutics at New York, March 29, 1934.¹ Preliminary reports were also made to the Society for Experimental Biology and Medicine.^{2,3}

ming, annually fumigates from 2000 to 3000 vessels in its quarantine work. Potassium cyanid or hydrocyanic acid is frequently used in photography, electroplating, metallurgy, and gilding, and must therefore be considered a potential danger to the lives of those who are engaged in such professions, unless adequate precaution is exercised.

Accidental deaths have resulted from eating nuts or other parts of plants that produce cyanophoric glucosids, such as bitter almonds. There are in the vegetable kingdom at least 360 varieties in 148 species and 41 families yielding hydrocyanic acid.

An arrow grass of the species *Triglochin maritima* has been fatal to livestock in Western States, due to its content of hydrocyanic acid. According to Beath, Draize and Eppson,⁴ the small shoots of regrowth collected at the end of September may assay as high as 77 mg. of hydrocyanic acid per 100 gm. of the green plant.

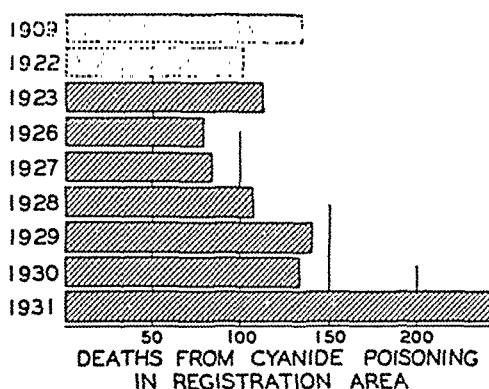


Fig. 1.

From 1909 to 1931 (Fig. 1) there have been 79 to 243 deaths annually from cyanid poisoning in the registration area of the United States. On the average, therefore, the mortality rate is about 1 to 2 per 1,000,000 population. In large cities, the death rate may be relatively higher. For example, in San Francisco, with a population of 634,394 in 1930, there were 8 deaths from cyanid poisoning in 1928, 10 in 1929, 11 in 1930, 12 in 1931, and 21 in 1932.⁵

The highest incidence of deaths from cyanid poisoning are due to suicide. Thus, in 1931 of the 243 deaths due to cyanid poisoning in the United States, 241 were suicidal. All the San Francisco deaths from 1928 to 1932 were also the result of self-murder.

Status of Previously Proposed Antidotes. A comprehensive review of the earlier literature on hydrocyanic acid and its derivatives and antidotes has been made by Hunt.⁶ It suffices here to mention the various chemical agents that have been advocated for the treatment of cyanid poisoning. One class of antidotes contains sulphur; of these sodium thiosulphate is the best known. The results of

Lang,⁷ Heymans and Masoin,⁸ Meurice,⁹ Hunt¹⁰ and Hug¹¹ indicate that sodium thiosulphate has to a certain degree some detoxifying effect in animals poisoned with a cyanid, particularly if it is introduced into the circulation beforehand. In spite of the limited efficacy of the thiosulphate therapy, favorable clinical reports have been made by Lassaga,¹² Feyerabend¹³ and Buzzo.^{14,15} In 2 cases of cyanid poisoning, sodium thiosulphate was injected intracardially.^{16,17}

Another sulphur-containing compound, sodium tetrathionate, was shown by Hebling,¹⁸ Chistoni and Foresti¹⁹ and Draize²⁰ to have an antidotal action against cyanid poisoning.

Evidence of antagonism between other sulphur-containing substances, such as sodium sulphid, cystin, cystein, thio-acetic acid, β -thiolactic acid, α - and β -dithiodilactylic acids, thioglycolic acid, glutathion, sodium seleniosulphate, and colloidal sulphur, on the one hand, and cyanid on the other, was furnished by Lang,⁷ Hebling,¹⁸ Voegtlin, Johnson, and Dyer,²¹ Meurice,²² Milanese²³ and Forst,²⁴ but from a practical point of view there is no indication that they are better than sodium thiosulphate.^{25,26}

Dihydroxyacetone injected prior to the poison affords protection in animals as reported by Forst,²⁴ Rentz,²⁷ and Turner and Hulpieu.²⁸ Similarly, glucose or glucose with insulin, administered beforehand, has been shown to exert an antagonistic action against cyanid by Violle²⁹ and others.^{30,31,32,24} On the contrary, Voegtlin, Johnson, and Dyer,²¹ Heymans and Soenen,³³ Hynd,³⁴ and Turner and Hulpieu²⁸ failed to notice any prophylactic value of glucose. A large number of other carbohydrates have been tested in cyanid poisoning by Forst,³⁵ but the majority of them are useless if poisoning has already taken place.

Although cobalt nitrate appears to have some protective value in animals against cyanid poisoning,^{36,7,9} it is itself a relatively toxic substance. Potassium permanganate and hydrogen peroxid might be expected to be efficient chemical antidotes of cyanid, but the results of Walko³⁷ and Muntsch³⁸ indicate nothing of practical importance. Certain depressants, such as scopolamin and morphin, may postpone the onset of convulsions, but they do not seem to reduce the toxicity of cyanid.^{39,27}

Circumstances Leading to Present Investigation. In 1932 Geiger⁴⁰ reported a case of cyanid poisoning successfully treated with methylene blue and, later, 2 other cases which recovered. The adoption of methylene blue therapy was based upon the work of Sahlin,⁴¹ Eddy,⁴² Brooks,⁴³ Hug¹¹ and Hanzlik.⁴⁴ Hug⁴⁵ and Wendel,⁴⁶ working independently, came to the conclusion that the antidotal action of methylene blue is due to the formation of methemoglobin which, in turn, reacts with the cyanid ion to form a much less toxic compound, cyanmethemoglobin.

Our primary interest in the problem was to ascertain quantita-

tively how many fatal doses of cyanid can be detoxified by methylene blue. In one paper, we showed that by the injection of the dye, animals were saved from 2 fatal doses.⁴⁷ Amyl nitrite given by inhalation, on the other hand, antidotes 4 fatal doses.

After the appearance of our paper,⁴⁷ it was our good fortune to learn by personal communication that an American physician, Doctor Pedigo,⁴⁸ in 1888 proved beyond doubt the value of amyl nitrite against cyanid poisoning in dogs. Unfortunately, his article has not been listed in easily available indices or mentioned in textbooks, so that it is difficult for later investigators to be aware of his important work. The delay in appreciating his results has probably also caused the tardy development of the nitrite therapy.

Another paper that deserves special mention is that of Mladoveanu and Gheorghiu⁴⁹ who in 1929 demonstrated the unquestionable benefit of sodium nitrite in both anesthetized and unanesthetized dogs during cyanid intoxication. Evidence was presented that this nitrite saved animals from several fatal doses of potassium cyanid.

Work was continued in our laboratory on other nitrites and sodium thiosulphate and tetrathionate. In view of the fact that none of the substances detoxified more than 4 lethal doses of cyanid, it was finally decided to try combination therapy, especially because a synergistic action was noted by Forst²⁴ with dihydroxyacetone and colloidal sulphur, and by Turner and Hulpieu²⁸ with dihydroxyacetone and sodium thiosulphate. Meanwhile, Hug⁵⁰ and Buzzo and Carratala⁵¹ made studies along the same line with reference particularly to the combination of sodium nitrite and sodium thiosulphate, and their reports have promptly appeared. In general, there is mutual confirmation of their results and ours.

Experimental Procedure. All the experiments were made on a group of 193 dogs weighing from 7 to 24.6 kg. (average 14.2), 186 of which were unanesthetized. In the early stages of the investigation, mice and rabbits were also employed, but they were found to be less suitable because of their relatively more rapid death from cyanid poisoning. In them, the various antidotes in order to be effective should be given preferably some time before the poison. In the dog, on the other hand, more precise results may be obtained and better comparisons can be made with different detoxifying agents. Furthermore, if a substance has a high antidotal action, it is almost always possible to demonstrate in dogs its efficacy during the late stages of cyanid poisoning; for example, immediately after respiratory failure.

The compounds studied in cyanid poisoning included methylene blue, nitroglycerin, amyl nitrite, sodium nitrite, sodium thiosulphate, sodium tetrathionate, combinations of sodium thiosulphate with sodium nitrite or amyl nitrite, and sodium tetrathionate with sodium nitrite or methylene blue. All of the substances, as well as sodium cyanid, were of the highest purity, conforming with U. S. P. requirements. The first lot of sodium tetrathionate, which is not official in the U. S. P., was courteously supplied by Dr. O. A. Beath, the Agricultural Experimental Station, University of Wyoming, to whom we are greatly indebted. The remaining amount of

sodium tetrathionate was prepared by ourselves, at Dr. Beath's suggestion, according to Biltz and Biltz (transl. by Hall and Blanchard).⁵²

In each unanesthetized dog, the antidotal agent was given slowly by vein at the same time the sodium cyanid gained entrance into the body (subcutaneously). In several cases the poison was administered first and promptly followed by the antidote. The recorded antidotal value can therefore be termed maximal for each substance or combination since it was estimated under the most favorable conditions. No prophylactic action was determined, that is, by giving the antidote beforehand, because it had no bearing on the practical therapy. Solutions of 4 to 10% of sodium cyanid were employed depending upon the size of the dose to be administered. The dog was observed continuously day and night, and its pulse and respiratory rates were counted at frequent intervals. When signs of poisoning, such as vomiting, convulsions, and respiratory or circulatory embarrassment, persisted for longer than the first hour or reappeared in

MEDICATION	NUMBER OF M.L.D.'S OF NaCN REQUIRED TO KILL
NONE	●
$C_3H_5(NO_3)_3$	●
METHYLENE BLUE	● ● ●
$Na_2S_2O_3$	● ● ● ●
$Na_2S_4O_6$	● ● ● ●
$C_3H_7NO_2$	● ● ● ● ●
$NaNO_2$	● ● ● ● ●
METHYLENE BLUE & $Na_2S_4O_6$	● ● ● ● ●
$C_3H_7NO_2$ & $Na_2S_2O_3$	● ● ● ● ● ● ●
$NaNO_2$ & $Na_2S_4O_6$	● ● ● ● ● ● ●
$NaNO_2$ & $Na_2S_2O_3$	● ● ● ● ● ● ● ● ● ● ● ● ●

FIG. 2.—Comparison of antidotal action of different substances in dogs.

the course of experimentation, the antidote was repeated in usually one-half of the initial dose. No animal was pronounced recovered until it was free from all signs of poisoning, accepted its food, and resumed its ordinary activity. Amyl nitrite was the only substance that was administered by inhalation, the technique of which was previously described.⁴⁷ A criterion of 3 out of 5 dogs was adopted in the majority of the cases to determine the highest dose of cyanid an antidote would detoxify.

Experiments were also carried out with sodium amytal, washed red blood corpuscles, insulin, glucose, and adrenalin, in the treatment of cyanid poisoning.

Results. Our data are summarized in Table 1 and illustrated in Figure 2. The minimal lethal dose (M.L.D.) of sodium cyanid in dogs by subcutaneous injection was determined to be 6 mg. per kg. of body weight. The results with antidotal medication may be discussed in Table 1, p. 772.

1. *Nitroglycerin.* This substance is not a true nitrite, although it has an action similar to that of a nitrite. In the present studies, 2 to 5% solutions in propylene glycol were employed. Dogs receiving 10 to 20 mg. per kg. all had violent convulsions but recovered. A dose of 5 mg. per kg. was not

TABLE 1.—COMPARISON OF ANTIDOTAL ACTION OF VARIOUS SUBSTANCES IN CYANID POISONING IN DOGS.

NaCN.		Antidotal medication.	Number of dogs used.	Number of dogs recovered.	Highest No. of M.L.D.'s of NaCN detoxified.
Mg. per kg.	M.L.D.				
5	0.8	None	3	2	0
6	1		10	2	
6	1	Methylene blue	2	2	2
12	2		4	3	
18	3		3	0	
12	2	Sodium thiosulphate	3	3	3
18	3		5	3	
24	4		3	0	
12	2	Sodium tetrathionate	5	3	3
18	3		3	3	
24	4		3	0	
18	3	Amyl nitrite	2	2	4
24	4		5	3	
30	5		6	0	
24	4	Sodium nitrite	5	3	4
30	5		5	2	
36	6	Methylene blue and sodium tetrathionate	1	1	6(?)
42	7		1	0	
48	8		1	0	
54	9		1	0	
60	10	Amyl nitrite and sodium thiosulphate	5	3	10
66	11		3	0	
72	12		3	0	
78	13		3	0	
72	12	Sodium nitrite and sodium tetrathionate	5	3	13
78	13		4	3	
84	14		5	2	
60	10	Sodium nitrite and sodium thiosulphate	4	3	20
72	12		4	3	
78	13		5	3	
120	20		7	4	
126	21		3	0	

able to detoxify 2 M.L.D.'s of sodium cyanid in animals—one dog died in 21 hours and 50 min., and the other in 38 min. There was little indication that nitroglycerin had an antidotal action.

2. *Methylene Blue*. A 1% solution of the dye, freshly prepared, was injected 1 to 5 min. after the cyanid. It should be noted from Table 1 that methylene blue in the dosage of 200 to 550 mg. per kg. can detoxify only 2 M.L.D.'s of sodium cyanid. Trautman⁵³ found that in rabbits methylene blue was useless in hydrocyanic acid gas poisoning. Furthermore, Sahlin⁴¹ emphasized the toxicity of methylene blue, and Macht and Harden⁵⁴ recently reported wide variations of toxicity in commercial samples of the dye, even though they were all labelled U. S. P. quality.

3. *Sodium Thiosulphate*. A 50% solution of this well-known substance, freshly made, was injected by vein. It was surprising that such a hypertonic solution, when carefully injected, did not cause any sloughing or local edema. The compound has a very low toxicity, for dogs receiving 3 gm. per kg. showed no signs other than vomiting during the first hour. In the dosage of 1 or 2 gm. per kg., sodium thiosulphate saved dogs from 3 M.L.D.'s of sodium cyanid.

4. *Sodium Tetrathionate*. This sulphur compound is less stable in aqueous solution (25%) than sodium thiosulphate, although it has the same antidotal value in a dosage of 500 mg. per kg. Sodium tetrathionate caused vomiting in dogs when doses of from 0.5 to 0.75 gm. per kg. were injected intravenously. A dose of 1.0 gm. per kg. killed; hence it is more toxic than sodium thiosulphate.

5. *Amyl Nitrite*. By repeated inhalations, dogs were saved from 4 M.L.D.'s of sodium cyanid as already described in a previous paper.⁴⁷ Some animals required as many as 102 inhalations.

6. *Sodium Nitrite*. Each morning a 4% aqueous solution was freshly prepared for the experiments of the day. The M.L.D. of sodium nitrite in dogs by rapid injection was found to be 45 mg. per kg. In cyanid poisoning one-half of the M.L.D. of the nitrite, that is, 22.5 mg. per kg., was given in the first dose, but it was reduced to 10 mg. per kg. in subsequent doses. Several dogs surviving the cyanid poisoning received total amounts of 72.5 to 92.5 mg. of sodium nitrite per kg. The efficacy of sodium nitrite is equal to that of amyl nitrite; that is, it antidotes 4 M.L.D.'s of sodium cyanid in the majority of cases.

7. *Methylene Blue and Sodium Tetrathionate*. In 5 dogs poisoned with sodium cyanid, methylene blue (200 mg. per kg.) was injected and immediately followed by sodium tetrathionate (500 mg. per kg.). Although the number of experiments was too small, yet the results seem to indicate that this combination at its best saves dogs from 6 M.L.D.'s of sodium cyanid. An additional animal was given 8 M.L.D.'s of the cyanid and treated with methylene blue and sodium thiosulphate, with no success.

8. *Amyl Nitrite and Sodium Thiosulphate*. Intravenous injection of sodium thiosulphate and repeated inhalations of amyl nitrite detoxified in dogs 10 M.L.D.'s of sodium cyanid, beyond which the combination became ineffective.

9. *Sodium Nitrite and Sodium Tetrathionate*. Dogs injected intravenously with sodium nitrite and then sodium tetrathionate, survived 13 M.L.D.'s of sodium cyanid. The initial dose consisted of 22.5 mg. of sodium nitrite per kg., and sodium tetrathionate, 500 mg. per kg., the subsequent doses being 10 and 250 mg., respectively. Recovery occurred even when the treatment was instituted after respiratory failure.

10. *Sodium Nitrite and Sodium Thiosulphate*. The best antidotal action was observed with successive injections of sodium nitrite and sodium thiosulphate (Fig. 2). It was found that the optimal initial dose of sodium nitrite was 22.5 mg. per kg., and that of sodium thiosulphate, 1.0 gm. per

kg. Subsequent doses of the nitrite should be 10 mg. per kg., and those of the thiosulphate, 0.5 gm. per kg. As shown in Table 1, 4 out of 7 dogs were saved from 20 M.L.D.'s of sodium cyanid by such medication. Death was delayed for several hours in those animals which did not survive. The efficacy of the nitrite-thiosulphate combination diminishes if the initial doses are either increased or decreased. For example, by injecting an initial dose of 22.5 mg. of sodium nitrite and 2.0 gm. of sodium thiosulphate, per kg. of body weight, only 13 M.L.D.'s of sodium cyanid were detoxified, as stated in our preliminary report.²

The action of sodium nitrite is prompt. It abolishes or decreases convulsions and often puts the poisoned dogs on their feet within a few minutes. Sodium thiosulphate, on the other hand, is comparatively slow in its effect, and does not appear to inhibit convulsive movements like the nitrite. One feature that was observed and should be pointed out is the conversion of a rapidly fatal course of cyanid poisoning to prolonged remissions with occasional reappearance of toxic signs. There was a period of stupor or depression following the use of the antidotes. The 4 dogs receiving 20 M.L.D.'s of sodium cyanid required from 42 to 47 hours for complete recovery under the nitrite-thiosulphate treatment. The nitrite and the thiosulphate should be repeated when there is an occurrence of vomiting, hyperexcitability, tremor, dyspnea, or tachycardia. Sometimes it is a wise measure to administer them prophylactically even in the absence of the signs. However, under no circumstances should they be repeated oftener than once per hour. As the experiment progresses the frequency must be greatly reduced, say, once every 3, 4, or 8 hours. Rapid accumulation of sodium nitrite is just as serious as cyanid poisoning for it increases the degree of asphyxia. Two of our surviving animals received total amounts of 122.5 mg. of sodium nitrite per kg., and 6 gm. of sodium thiosulphate per kg. in 11 doses.

The beneficial effect of the nitrite-thiosulphate therapy is convincingly demonstrated in Figure 3. The dog on the left hand side received 1 M.L.D. of cyanid. It vomited repeatedly 9 min. after the injection of the poison, went into convulsions in 21 min., and died in 53 min. The dog on the right hand side had 10 M.L.D.'s of cyanid. Following the poison sodium nitrite and sodium thiosulphate were injected in order. The dog vomited once 23 min. after the introduction of the poison, but it was able to stand up on its feet practically all the time. To insure complete detoxification of the cyanid, the nitrite and the thiosulphate were repeated in 1 hour 50 min., and 3 hours 50 min. The dog appeared perfectly normal in 20 hours 35 min. The experiment could not be duplicated with methylene blue, sodium nitrite alone, or sodium thiosulphate alone.

The antidotal action can be illustrated in another manner. In Figure 4, the respiratory movements of an anesthetized dog are graphically recorded. At the beginning of the experiment a volume

of 4 cc. of the cyanid (M/50) was injected by vein in the course of 1 min. This was followed by the familiar respiratory stimulation which, according to Heymans, Bouckaert and Dautrebande,⁵⁵ is due chiefly to carotid sinus reflexes. Upon the return of the respiration to the initial rate and amplitude, a 1% solution of sodium nitrite was injected intravenously at the rate of 4 cc. per min. until a dose of 22.5 mg. per kg. had been reached. The injection was then continued with a 50% solution of sodium thiosulphate at the same rate until a quantity of 1 gm. per kg. had been administered. The resumption of sodium cyanid at the rate of 4 cc. per min. after









TIME AFTER INJECTION	1 M.L.D. NACN	10 M.L.D. NACN + NaNO_2 & $\text{Na}_2\text{S}_2\text{O}_3$
0 MIN.		
9 MIN.		
21 MIN.		
53 MIN.		

FIG. 3.—Contrast of treated and untreated animals. Dog on the left-hand side, male, weighed 13.7 kg. and received subcutaneously 6 mg. of sodium cyanid per kg. of body weight. Dog on the right-hand side, male, weighed 14.8 kg. He was given 60 mg. of sodium cyanid per kg. Simultaneously with the poison, sodium nitrite in the dosage of 22.5 mg. per kg. was injected intravenously, and followed by 2 gm. of sodium thiosulphate per kg. See text for further details.

the thiosulphate now produced no respiratory stimulation. When more than 2 M.L.D.'s of sodium cyanid had been given (the M.L.D. in anesthetized dogs by intravenous injection is approximately 3 cc. of M/50 solution per kg.), the amplitude of the respiration became gradually larger. The dog stopped breathing after 8 M.L.D.'s of the cyanid had been introduced. The same experiment was made with 6 other anesthetized dogs, and the results were confirmatory of those just described. The total amount of the cyanid required to kill those animals varied from about 6 to 9 M.L.D.'s.

To give a crucial test of the nitrite-thiosulphate therapy, a few dogs were injected with large doses of sodium cyanid, and allowed to develop dangerous signs of poisoning, such as convulsions, loss of corneal reflex, and in 1 case cessation of respiration, although the heart was still beating. It was found that, by the intravenous injection of the nitrite and the thiosulphate after the appearance of these dangerous signs, several dogs were revived from 10, 13, and 15 M.L.D.'s of the cyanid. It did not seem possible to save dogs that had been poisoned for some time with 20 M.L.D.'s of cyanid. This is to be expected because the efficacy of an antidote diminishes as poisoning becomes well advanced.

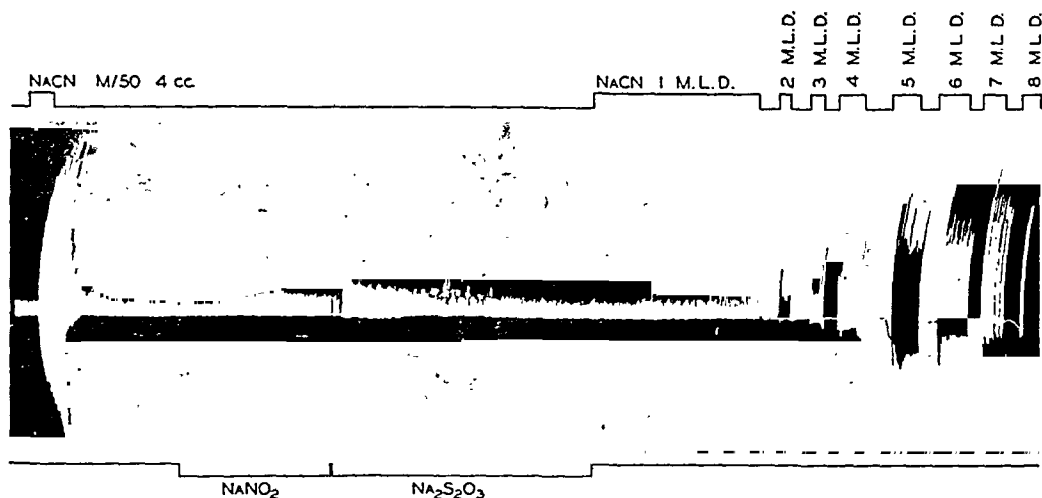


FIG. 4.—Detoxification of cyanid as shown on respiration. Dog, female, weighing 9.3 kg., was anesthetized with phenobarbital sodium subcutaneously, 0.15 gm. per kg. The tracing of respiration should be read from left to right. After the first M.L.D. of sodium cyanid had been injected, the drum was stopped. At the end of the second M.L.D., it was started again for a short distance, and so on until the animal died. See text for explanation.

Hug⁵⁰ reported that dogs receiving 6 M.L.D.'s of hydrocyanic acid were saved with sodium nitrite and sodium thiosulphate. He further stated that if hydrocyanic acid was injected by vein at the rate of 0.2 mg. per kg. per minute, dogs died with a dose of 0.8 mg. per kg.; but if sodium nitrite and sodium thiosulphate were administered, more than 8 mg. of the poison per kg. were detoxified. Buzzo and Carratala⁵¹ claimed that in rabbits sodium nitrite and sodium thiosulphate injected intravenously antidoted 18 M.L.D.'s of potassium cyanid which was given by mouth. This work needs confirmation, particularly because of the fact that according to these authors¹⁴ sodium thiosulphate alone overcame 10 M.L.D.'s of cyanid—a figure twice as great as that observed by Lang⁷ under the same conditions. In our own laboratory, no rabbits treated with the nitrite and the thiosulphate survived more than 6 M.L.D.'s of cyanid which was injected subcutaneously.

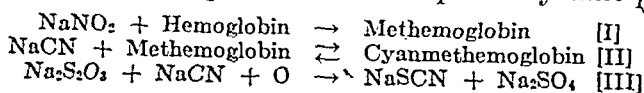
11. *Miscellaneous.* Two dogs poisoned with 5 M.L.D.'s of sodium cyanid, but treated with amyl nitrite, were injected intravenously with washed red blood corpuscles, prepared from another dog, with the hope that the added amount of hemoglobin would increase the capacity of detoxification. Although the transfusions prolonged the surviving period, they did not alter the outcome of the experiments, that is, the animals finally died. Hematuria promptly appeared. An anesthetic dose of sodium amytal with no other medication was injected by vein into another dog receiving 2 M.L.D.'s of cyanid. Convulsions did not occur but respiration failed in 22 min. The suppression of convulsions alone contributed no benefit to the course of cyanid poisoning. There was another dog that had 5 M.L.D.'s of sodium cyanid and received, in addition to amyl nitrite inhalations, insulin and glucose. It died in 1 hour 6 min. There was no evidence that glucose and insulin had any favorable influence upon cyanid poisoning. During the terminal stages of two additional experiments, adrenalin was given intravenously, but it failed to delay the fatal outcome. Obviously, stimulation of the circulation did not postpone the respiratory failure.

Discussion. Of the list of substances that have an antidotal action in cyanid poisoning (Table 1), methylene blue has the least efficacy. Sodium thiosulphate and sodium tetrathionate are equal in value. Amyl nitrite and sodium nitrite are both twice as effective as methylene blue. The most interesting feature is the synergism and potentiation of action of the nitrites on the one hand and the sulphur compounds on the other. The combination of sodium nitrite and sodium thiosulphate detoxified 20 M.L.D.'s of sodium cyanid, which is almost 3 times the sum of their individual values, and fully 10 times as effective as methylene blue alone. A slight potentiation of action also appears to exist between methylene blue and sodium tetrathionate.

No attempt was made to determine the mechanism of cyanid detoxification in this investigation, but there has been a sufficient accumulation of published data to warrant a tentative explanation. It is well known that nitrite ions react with hemoglobin. Hug^{45,56} and Wendel⁴⁶ recently pointed out that the formation of cyanmethemoglobin by cyanid ions and methemoglobin accounted for the detoxification of the cyanid. Previously, Rosenthal and Voegtlin⁵⁷ had already observed an antagonism between methemoglobin and cyanid on the rat testis (Warburg's apparatus). The pigment cyanmethemoglobin was first prepared by Kobert⁵⁸ and crystallized by Zeynek.⁵⁹ According to Barnard⁶⁰ cyanid combines with the iron of the methemoglobin molecule. Cyanmethemoglobin must be many times less toxic than cyanid.

Another mode of detoxification, the conversion of cyanid to sulphocyanate, has been suggested by numerous workers. Sulphocyanate is a relatively harmless radical. It is normally found in salivary secretions.

In the combined action of sodium nitrite and sodium thiosulphate, then, the following three reactions probably take place:



When the nitrite is injected alone, the sulphur is furnished by the thio-constituents of the body, such as cystein, glutathion, etc. It is not improbable that the chief function of the nitrite is to pick out the cyanid from various tissues and convert it to cyanmethemoglobin *via* methemoglobin. The real detoxification of the cyanid is its conversion to sulphocyanate, which is mainly brought about by the sodium thiosulphate administered, and to a less extent by the cystein and glutathion of the body. Recently Lang⁶¹ demonstrated that the formation of sulphocyanate in the organism was catalyzed by an enzyme to which he gave the name rhodanase. When sodium nitrite and sodium thiosulphate are used together, it seems that the speed of conversion from cyanid to sulphocyanate is much accelerated. This results in the potentiation of the antidotal action of these two substances. On the other hand, equation [II] may be reversible so that in course of time free cyanid ions are liberated and typical poisoning signs reappear. Meanwhile, part of the sodium thiosulphate may have been eliminated. This explains the necessity for repeating the antidotes during the course of an experiment.

The above explanation does not exclude other methods of cyanid detoxification, but as far as the evidence goes the formation of cyanmethemoglobin and sulphocyanate probably plays the most important rôle.

A question arises as to why all the nitrites, as well as methylene blue, do not have the same degree of potentiation of action since each compound forms methemoglobin with hemoglobin. It must be recognized, however, that the similarity of this group of substances is only qualitative. The effect of amyl nitrite is quick but brief, and that of sodium nitrite slower but more prolonged. The convulsant action of nitroglycerin is synergistic with that of cyanid. According to Hug⁵⁶, a dose of 40 mg. of sodium nitrite per kg. converts 56 to 83% of hemoglobin to methemoglobin. Methylene blue, on the other hand, has a lower capacity of forming methemoglobin⁶²—so much so that it was not possible to demonstrate the presence of methemoglobin in the blood of poisoned cases.⁴⁰ Amyl nitrite alone has the same antidotal action as sodium nitrite, but in association with sodium thiosulphate it does not potentiate as much as the latter. Buzzo and Carratala⁶³ obtained similar results in rabbits. The question of methemoglobin concentration may also be concerned with the difference of action here.

The favorable results of the nitrite-thiosulphate therapy in dogs against cyanid poisoning warrant trials in human cases, especially because both sodium nitrite and sodium thiosulphate are well known in medicine. Mota⁶⁴ has already saved a case of cyanid poisoning with sodium nitrite, the total amount injected being 0.57 gm. The temporary depressor action apparently caused no damage. As pointed out above, sodium thiosulphate has also been employed for the same purpose. While the most suitable dosage of the combination remains to be established, we would suggest

using 6 to 10 mg. of sodium nitrite per kg., and 0.5 gm. of sodium thiosulphate per kg. For an adult of 50 kg., therefore, the first dose would consist of 0.3 to 0.5 gm. of sodium nitrite and 25 gm. of sodium thiosulphate. Subsequent doses should be one-half of that quantity. The two substances must not be mixed for administration.

It may be reiterated here that the prognosis of any case of cyanid poisoning depends upon the dose of the poison taken and the promptness of treatment—the earlier the better. Assuming that the quantity of cyanid absorbed is not too great, a rational treatment, based on animal experiments, would be: (A) immediate administration (inhalation) of amyl nitrite by an assistant for from 15 to 30 sec., to be repeated every 2 to 3 min. until the physician has filled his syringes with the antidotal solutions; (B) intravenous injection of sodium nitrite at the rate of 2.5 to 5 cc. per minute, followed by sodium thiosulphate at the same rate, care being taken to avoid extravasation; (C) gastric lavage if the poison is taken by mouth—preferably done by another physician for division of labor; (D) continuous observation of the patient for at least the first 24 to 48 hours. A temporary improvement of the patient's condition after initial medication does not insure ultimate recovery or indicate discontinuance of watching. When signs of poisoning persist or reappear 1 hour after the initial dose, the nitrite and the thiosulphate may be repeated. If there is no indication for repeating the antidotes, a second injection may be given 2 hours after the first for prophylactic purposes.

A kit for the treatment of cyanid poisoning should be prepared and installed in ambulances and emergency units of large hospitals. This should consist of:

- 12 Pearls of amyl nitrite
- 2 Ampules of sodium nitrite, 0.3 gm. in 10 cc. of water
- 2 Ampules of sodium thiosulphate, 25 gm. in 50 cc. of water
- 1 Sterile syringe, 10 cc. size, with a 22-gauge needle
- 1 Sterile syringe, 50 cc. size, with an 18-gauge needle
- 1 File
- 1 Stomach tube

During recent years, studies have been made to find substitutes for hydrocyanic acid for the fumigation of ships.^{65, 66} If, however, hydrocyanic acid continues to be used for fumigation, some efficacious antidote, such as the kit proposed above, should be provided either on the ship or conveniently located at the dock. It may be reminded that the fatal course of poisoning by hydrocyanic acid gas is shorter than that by its salts, potassium or sodium cyanid, so that therapeutical measures must be instituted immediately.

In agriculture, the veterinarian may try out the same dose of sodium nitrite and sodium thiosulphate as proposed for men for sheep poisoned with arrow grass. In horses and cattle, multiples of the same should be employed.

Summary. An antidotal action against cyanid poisoning is possessed by methylene blue, sodium thiosulphate, sodium tetrathionate, amyl nitrite, and sodium nitrite.

A potentiation of antidotal action occurs when a nitrite or methylene blue on the one hand, and sodium thiosulphate or sodium tetrathionate on the other, are successively administered.

The highest antidotal action is exhibited by the combination of sodium nitrite and sodium thiosulphate. Under the most favorable conditions in dogs, this combination detoxifies 20 minimal lethal doses of sodium cyanid, and is 10 times as effective as methylene blue. Recovery has occurred even when the two substances are given at the late stages of cyanid poisoning.

A technique for employing sodium nitrite and sodium thiosulphate in clinical trials has been suggested.

We wish to express our thanks to Messrs. Robert C. Anderson, Davis Rawlings, Robert Fink, Hans Schulze, Leo J. Freihage, John Hansen, William Winchester and Herschell Griffin for their assistance in numerous experiments.

ADDENDUM. While this manuscript was going to press there appeared two papers, one by Viana, Cagnoli and Cendan⁶⁷ and the other by Hanzlik and Richardson.⁶⁸ The former article was on 2 cases of cyanid poisoning successfully treated with the same antidotes we are proposing. The first case was that of a young girl who took 5 gm. of potassium cyanid. She received 1 ampule of amyl nitrite and a total amount of 1.5 gm. of sodium nitrite and 18 gm. of sodium thiosulphate. Although she developed severe cyanosis, recovery occurred. The second patient, a woman, ingested 2 gm. of potassium cyanid. She was administered 1 ampule of amyl nitrite and a total quantity of 0.75 gm. of sodium nitrite and 12 gm. of sodium thiosulphate. She also survived. In the report of Hanzlik and Richardson, they presented data on sodium nitrite and sodium thiosulphate, confirmatory of our results, but they argued that methylene blue should be considered the antidote of first choice in cyanid poisoning.

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ON THE INHERITANCE OF DIABETES MELLITUS.

III. THE BLOOD SUGAR VALUES OF THE RELATIVES OF DIABETICS.

BY GREGORY PINCUS, Sc.D.,

ASSISTANT PROFESSOR OF GENERAL PHYSIOLOGY, HARVARD UNIVERSITY,

AND

PRISCILLA WHITE, M.D.,

PHYSICIAN, NEW ENGLAND DEACONESS HOSPITAL,
BOSTON, MASS.

(From the Laboratory of General Physiology, Harvard University, and the George F. Baker Clinic at the New England Deaconess Hospital.)

THE analysis of the genetic basis of diabetes susceptibility indicates that a number of apparently normal relatives of diabetics are in fact potential diabetics.^{1,2} The identification of these persons, destined because of their genetic constitution to develop the disease, is of some consequence from both a practical and a theoretical point of view. We have accordingly determined the blood sugar concentrations of 169 close relatives of known diabetics, on the assumption that abnormal concentrations might yield a clue to the presumable potential diabetics among them. In order to determine the limits of normal blood sugar concentrations we also examined a group of 125 control individuals.

Two sets of examinations were employed: (1) A set of routine venous blood sugar determinations, ordinarily taken 2 or more hours after a meal, and (2) a set of glucose and sucrose tolerance tests. These two groups of examinations will each be presented separately and then the relation of our findings to the Mendelian basis of the disease will be discussed.

Routine Blood Sugar Determinations. In Fig. 1 we present graphically the various blood sugar concentrations determined for 76 controls and an equal number of relatives of diabetics; also the statistical constants of these data. The control individuals are a group of non-diabetic patients *none of whom* had any immediate family history of diabetes. It will be noted that the mean blood sugar concentration in this group is 94.2 mg. per 100 cc. compared with a mean value of 101.3 for all the relatives of diabetics. A χ^2 comparison of the data of Fig. 1 gives a value of $P = 0.01$. This indicates a significant difference between the distribution of blood sugar values in the two groups. It is obvious from inspection of Fig. 1 that this difference is largely due to the presence of a number of abnormally high blood sugar concentrations in the experimental series.* Eleven (14.5%) of the values in the experimental

* Not only are the frequency distributions significantly different in our two series, but also the variance, *c. g.*, the ratio $\frac{\sigma_1^2}{\sigma_2^2}$ is 5.25. For $P = 0.01$ this ratio is 3.29 (see Snedecor³) and P is, therefore, much less than 0.01 in this series.

series lie at 140 or beyond in Fig. 1. If the experimental series represented a normal group of persons exactly comparable to our control series we should expect 0.37% of the determinations to lie at 140 or beyond. We can designate as a "limiting hyperglycemic value" 138.2 mg. per 100 cc. of blood, since blood sugar concentrations higher than that would occur once in 200 trials.*

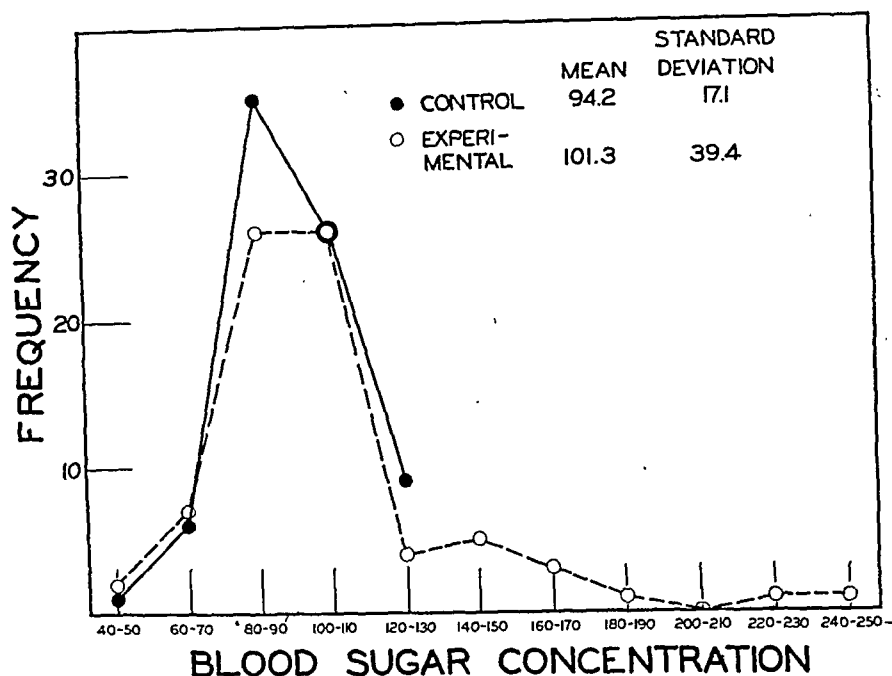


FIG. 1.—Frequency distributions for blood sugar concentrations in routine blood sugar determinations taken upon a control series and upon a series of relatives of diabetics. Blood sugars are given in mg. per 100 cc. of blood.

It may be objected that high blood sugar concentrations are encountered in non-diabetic persons of advanced age, and that the exceptional cases in our series represent elderly persons. This is not the case. The median age of the 11 exceptional persons is 34 years, and 9 of them are below 40 years of age. In fact, the population from which our standard control values are derived is a much more elderly group than our experimental series; the median age of the control series is about 50 years, that of the experimental series 26 years, so that our control data are definitely biased against the experimental data if the age factor is important. Actually, our control series does give a slight indication that the routine blood sugar values are slightly higher in older persons: of the 36 persons less than 50 years of age, 24 (66.66%) had blood sugar concentrations of less than 100 mg. per 100 cc., and of the 40 persons

* A value of 15 or above would occur less than once in 1000 trials, and a value of 16 or above once in 10,000 trials, yet we observe 9 of the former and 7 of the latter in these 76 observations.

above the age of 50, only 18 (45%) had blood sugar concentrations below 100 mg. per 100 cc. The difference is significant statistically (difference = 21.66%—probably error of difference = 5.3%, difference / PED = 4.07).

Sugar Tolerance. The 49 individuals employed as controls for the sugar tolerance series were normal healthy persons with no diabetic histories. Their median age was closer to that of the 95 relatives of diabetics given similar tests; the median ages in the two groups were 28 and 31 years, respectively.

Both glucose and sucrose tolerance tests were given: 100 gm. of glucose or 75 gm. of sucrose were taken 2 or more hours after a meal. No significant difference was found in the blood sugar values in the two tests. A definitely significant difference was observed between capillary and venous bloods, however, and accordingly the control series was divided into two groups: (1) 21 individuals whose capillary blood sugar concentrations were measured, and (2) 28 individuals whose venous bloods were taken. The capillary bloods were taken chiefly from very young and very old persons.

TABLE 1.—MEAN BLOOD SUGAR CONCENTRATIONS IN A SERIES OF CONTROL SUGAR TOLERANCE TESTS.

Hours after sugar ingestion.	Blood sugar concentration (mg. per 100 cc.).		Standard deviation (\pm mg. per 100 cc.).	
	Venous.	Capillary.	Venous.	Capillary.
0	74	98	84	139
$\frac{1}{2}$	103	146	248	201
1	85	126	275	180
2	75	102	155	182

The statistical constants of the data for the various determinations in the control series are given in Table 1 and in Fig. 2. Again, if we set as the limiting hyperglycemic value a blood sugar concentration equal to the mean value plus $2.5768 \times \sigma$, we observed at once that in our experimental series there are a number of high blood sugar concentrations (Table 5). These are summarized in Table 2.

TABLE 2.—THE NUMBER OF "SUPERNORMAL" BLOOD SUGAR VALUES AT VARIOUS TIMES DURING THE SUGAR TOLERANCE TESTS OF DIABETIC RELATIVES.

Time.	Total No. of determinations.	No. of "supernormal" values.	"Supernormal," per cent.
0	62	5	8.1
$\frac{1}{2}$	95	11	11.6
1	94	7	7.4
2	91	10	11.0
Totals	342	34	9.9

Actually the 34 "supernormal" values were obtained from 24 individuals, some of whom gave abnormally high values more

than once. These 24 individuals represent 25.3% of the 95 tested. In our control series of 49 persons a "supernormal" value was encountered only once (at the 2d hour) and then in a postoperative patient. The sugar tolerance tests revealed more "supernormal" persons than the routine blood sugar determinations. An inspection of Table 2, however, reveals that the percentage of "hyperglycemic" values was about the same at 0 hours as at $\frac{1}{2}$, 1 and 2 hours. This we believe to be deceptive, since the highest values were encountered after sugar ingestion (see Table 5). If we discount the 0 hour determinations, 19 individuals (20%) showed "supernormal" blood sugar concentrations after sugar ingestion.

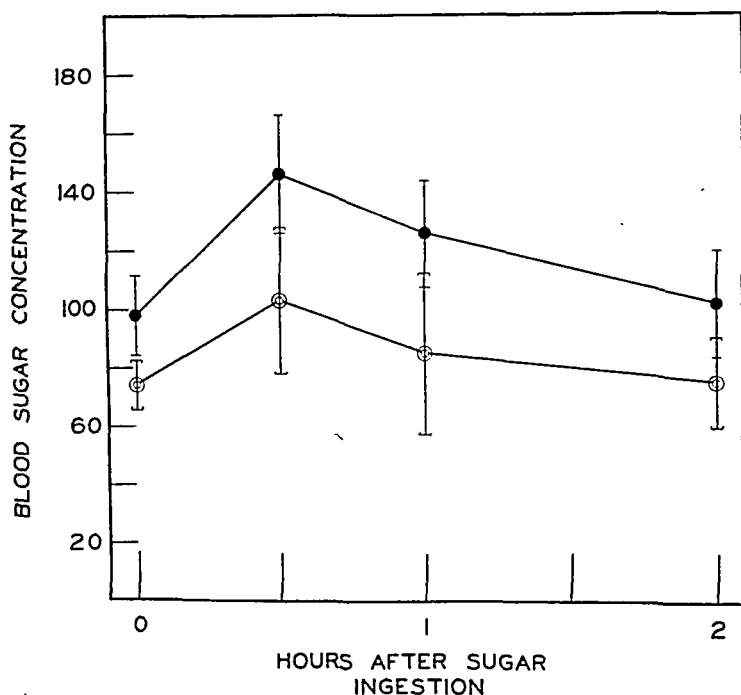


FIG. 2.—Mean blood sugar values (in mg. per 100 cc. of blood) for venous (open circles) and capillary (closed circles) bloods in control groups of normal, healthy persons. The vertical lines above and below the mean values are equal to the standard deviations of these values (Tables 1 and 4).

The Results of Blood Sugar Determinations in Various Types of Matings. Our assumption that diabetes will develop in persons homozygous for a recessive gene (*e. g.*, *mm* individuals) requires that *all* the offspring of 2 diabetic parents should one day develop diabetes (since the matings are *mm* × *mm*). We have, therefore, taken special pains to collect information on the families of as many conjugal diabetics as possible and have found 33 such families with a recorded total of 138 offspring. Of the children in these families, 20 have had either tolerance tests or routine blood sugar examinations. Of these 20, 5 gave hyperglycemic values, but 15

gave normal blood sugar values (see Table 3). If our Mendelian assumptions are correct this means that neither routine blood sugar determinations nor tolerance tests will give a clue to *all* the potential diabetics; nor would we expect such tests to reveal all potential diabetics, since it is well known that persons with completely normal tolerance curves may, at varying times after the test is given, develop diabetes. It is interesting to inquire, however, to what extent the discovery of hyperglycemia may be taken to indicate genetically diabetic individuals.

We arrange the classifiable matings as follows: (1) Neither parent diabetic; (2) one parent diabetic; (3) both parents diabetic. Matings (3) must on our Mendelian hypothesis be $mm \times mm$. Matings (1) and (2) may be taken provisionally as $Mm \times Mm$ and $Mm \times mm$, respectively, since they produced at least 1 diabetic child; but it must be kept in mind that a few of the parents in each group who are non-diabetic may be mm , since they have not developed diabetes though destined to do so. In Table 3 (see Table 6 for the age incidence relations) we summarize the diabetes incidence among the children in these various groups of matings, the extent of hyperglycemia and the expectation of diabetics on the basis of the life tables for potential diabetics presented in our previous paper.² (Tables 1 and 2.) The expectations for the $mm \times mm$ matings are immediately applicable to the observations, since we have no way of estimating the missing mm parents in the other two groups of matings.* As in our previous analysis, Joslin's incidence data call for a relatively high incidence compared to the more generalized incidence data based on Massachusetts incidence. The observations in the $mm \times mm$ matings do not depart significantly from either set of expectations, though again they agree more closely with the expectations based on Massachusetts incidence.

But the most interesting relation established by the data of Table 3 is the proportion of hyperglycemic individuals in the three types of matings. In the matings designated $Mm \times Mm$ (carrier \times carrier), 6.8% of the tested non-diabetic offspring were hyperglycemic, in $Mm \times mm$ (carrier \times diabetic), 17.9%, and in $mm \times mm$ (diabetic \times diabetic), 25%. These percentages are in the ratio 1:2.6:3.7. Now the simple Mendelian probabilities for such matings are in the ratio 1:2:4 (*e. g.*, $\frac{1}{4}:\frac{1}{2}:1$), and the ratios of presumed unidentified mm individuals are 1:2.2:3.9 on the basis of Joslin's onset data and 1:2.1:4.7 on the basis of the Massachusetts tables. If the "hyperglycemic" blood sugar examinations indicate merely the random distribution of peculiar individuals, then we should expect the percentages of "hyperglycemics" in the various matings to be in the ratio 1:1:1. Actually the number of

* In our previous analysis,^{1,2} we were able to do this, since the families were successive families appearing for treatment. The families in this series were selected for examination, particularly the $mm \times mm$ group.

TABLE 3.—THE INCIDENCE OF DIABETES AND HYPERGLYCEMIA AMONG THE CHILDREN IN VARIOUS TYPES OF MATINGS AND THE EXPECTATION OF DIABETES ON THE ASSUMPTION THAT DIABETES DEVELOPS AS A RECESSIVE CONDITION.

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Type of mating.	Total No. children.	No. of diabetic children.	No. of "hyperglycemic" children revealed by exam.	No. of children tested for "hyperglycemia."	Per cent "hyperglycemic."	Diabetic children expected (Joslin data).	Diabetic children expected (Mass. data).	Diabetic sibs observed.	Diabetic sibs expected (Joslin).	Diabetic sibs expected (Mass.).
Neither parent diabetic ($Mm \times Mm$)	126	49	3	44	6.8	45.38	44.12	6	2.38	1.12
One parent diabetic ($Mm \times mm$)	95	27	7	39	17.9	23.19	22.06	7	3.19	2.06
Both parents diabetic ($mm \times mm$)	138	30	5	20	25.0	41.49	22.40	—	—*	—*

* These expectations are not calculated, since the families were selected because both parents were diabetic. The expectations of columns (7) and (8) should be compared directly with the observed number in column (3).

TABLE 6.—SUMMARY OF THE INCIDENCE OF DIABETES AND HYPERGLYCEMIA IN VARIOUS MATINGS.

Decade.	Neither parent diabetic.					One parent diabetic.					Both parents diabetic.				
	Diabetic patients.	Diabetic sibs.	Non-diabetic sibs.	Hyper-glycemic sibs.	Siblings tested for hyper-glycemia.	Diabetic patients.	Diabetic sibs.	Non-diabetic sibs.	Hyper-glycemic sibs.	Siblings tested for hyper-glycemia.	Diabetic children.	Non-diabetic children.	Hyper-glycemic children.	No. of children tested.	
1	31	1	34	1	17	6	1	10	2	6	1	24	—	1	
2	9	1	30	2	24	5	1	11	3	10	3	6	—	3	
3	1	2	6	..	3	2	—	22	—	15	—	15	1	6	
4	—	—	1	4	2	8	1	5	2	29	4	9	
5	—	1	—	1	1	4	1	2	10	11	..	1	
6	1	—	1	1	2	4	9	6	
7	1	—	1	1	..	2	4	8	
8	..	1	1	1	3	
Totals	43	6	74	3	44	20	7	61	7	39	30	103	5	20	

observations is too small to give any exact significance to these ratios;* but the result is suggestive, indicating that these hyperglycemic individuals *may* be potential diabetics (*e. g.*, *mm* individuals). A larger series would undoubtedly resolve this possibility.

If we assume that these hyperglycemic individuals do represent

TABLE 4.—SUMMARY OF BLOOD SUGAR CONCENTRATIONS IN TOLERANCE TESTS ON A CONTROL POPULATION.

Blood sugar (mg. per 100 cc.)	Hours after sugar ingestion.							
	0	0	$\frac{1}{2}$	$\frac{1}{2}$	1	1	2	2
	Venous.	Capillary.	Venous.	Capillary.	Venous.	Capillary.	Venous.	Capillary.
40 to 50	1	...	2	
60 to 70 . . .	15	2	4	...	12	...	17	1
80 to 90 . . .	12	3	8	...	8	...	4	7
100 to 110	13	7	...	3	7	3	7
120 to 130	1	6	7	2	8	1	5
140 to 150	3	9	2	5		
160 to 170	3	...	1		
180 to 190	2				
Totals . . .	27	19	28	21	28	21	27	20

TABLE 5.—SUMMARY OF BLOOD SUGAR CONCENTRATIONS IN TOLERANCE TESTS ON RELATIVES OF DIABETICS.

Blood sugar (mg. per 100 cc.)	Hours after sugar ingestion.							
	0	0	$\frac{1}{2}$	$\frac{1}{2}$	1	1	2	2
	Venous.	Capillary.	Venous.	Capillary.	Venous.	Capillary.	Venous.	Capillary.
40 to 50 . . .	1	2	
60 to 70 . . .	11	...	3	...	11	...	31	
80 to 90 . . .	41	...	8	...	25	1	26	2
100 to 110 . . .	7	1	24	...	17	—	16	1
120 to 130 . . .	1	...	23	2	16	2	7	1
140 to 150	17	2	10	1	—	1
160 to 170	7	4	4	4	1	1
180 to 190	2	—	—	...	—	
200 to 210	2	1	1	...	—	
220 to 230	1	...	—	1
240+	1†	...	1‡	
Totals . . .	61	1	86	9	86	8	84	7

* A value of $P < 0.05$ is obtained on a χ^2 test for independence. This indicates a probably significant difference between the three groups.

† 320 mg. per 100 cc.

‡ 350 mg. per 100 cc.

future diabetics, then we can determine roughly the extent of prediction of diabetes that these tests afford. Taking the $mm \times mm$ cross alone, 25% of the children examined were hyperglycemic; then presumably a similar percentage would be revealed among the children we did not examine. We would expect to find 25 additional hyperglycemic individuals, or a total of 30 among 108 individuals listed as non-diabetic. If, for the moment, we assume that these 30 individuals are "diabetic," then there is revealed a total of 60 diabetics among the 138 offspring, or about 45% in a group of potential diabetics whose median age is 35 years. On the Massachusetts incidence data this is the percentage we would expect to identify as diabetic in a completed population (subject to 1920 death rates) with a median age of about 53 years (and on Joslin's data at a median age of about 48 years). Thus our blood sugar examinations may be taken to have enabled us to foretell by many years the future diabetics. We can make no exact calculations of the extent of this anticipation, since we would have to employ the hazardous procedure of determining the distribution of age at onset of diabetes in a population destined to live beyond age 90, and, furthermore, we would have to make other assumptions about the random occurrence of hyperglycemia which cannot be made until the relation of hyperglycemia to the age of tested individuals is established.

Discussion. Obvious obstacles prevent the collecting of the rather large set of data that would permit a completely satisfactory statistical resolution of the significance of the presence of hyperglycemic individuals in diabetic families. None the less it is clear that an excessive number of high blood sugar values do occur in such families when comparison is made with a carefully collected control series. We would like to stress here that the blood sugar values that we have termed hyperglycemic are *not* necessarily diabetic blood sugar values; they are abnormal on the basis of our control series. To establish the limits of diabetic blood sugars we should have a series of exact determinations of blood sugar values among persons with uncontrolled diabetes; this we do not have, and, on *a priori* grounds, it seems highly doubtful that such a series could be satisfactorily assembled. But our investigation does indicate that the establishment of a set of "normal" blood sugar values require the strict exclusion of near relatives of diabetics. Therefore, any calculation of "normal" values based upon data not so guarded is open to criticism if it is used to set a limit to normality. Even when careful inquiry reveals no family history of diabetes there always exists the possibility that undetected potential diabetes is present in certain families. More delicate tests for latent diabetes would, of course, obviate much of the purely formal difficulties here presented. It is hoped that such tests may be available.

Summary. Approximately 14% of a group of relatives of diabetics given routine blood sugar examinations and 25% of those given sugar tolerance tests had abnormally high blood sugar values when comparison is made with similar determinations made upon control groups of normal healthy persons with no family history of diabetes incidence. When we examine, in various types of matings, the incidence of such "hyperglycemic" persons among the offspring, the data suggest that such individuals may be taken as future diabetics, since the ratios of them in these matings are approximately proportional to the ratios of presumed unidentified genetically diabetic individuals called for by the Mendelian hypothesis advanced to explain the inheritance of diabetes. These tests do not, however, reveal all the genetically diabetic individuals. It is pointed out that if these tests have any general significance, they indicate that the establishment of normal blood sugar values requires the strict exclusion of relatives of diabetics from the group of normal persons supplying the data.

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CARBOHYDRATE METABOLISM IN HUMAN HYPOTHYROIDISM INDUCED BY TOTAL THYROIDECTOMY.*

I. THE GLUCOSE TOLERANCE CURVE AND THE FASTING SERUM SUGAR CONCENTRATION.

BY D. ROURKE GILLIGAN, M.S.,

RESEARCH FELLOW IN MEDICINE, HARVARD MEDICAL SCHOOL,

MAURICE I. ABRAMS, M.D.,

ASSISTANT IN MEDICINE, HARVARD MEDICAL SCHOOL,

AND

BEATRICE STERN, A.B.,

RESEARCH ASSISTANT, BETH ISRAEL HOSPITAL, BOSTON, MASS.

(From the Medical Research Laboratories of the Beth Israel Hospital, and the Department of Medicine, Harvard University Medical School.)

INVESTIGATIONS concerning the effect of hypothyroidism on carbohydrate metabolism in man have given rise to varying opinions. The fasting blood sugar in non-diabetic patients with hypothyroid-

* This investigation was aided by a grant from the William W. Wellington Memorial Research Fund of Harvard University.

ism has been found normal^{3,4,5} or low.^{4,6} After glucose administration in non-diabetic patients with hypothyroidism, some authors have found a normal response;¹ others have found a subnormal rise in blood sugar;^{2,3} while still others have concluded that the blood sugar rises higher and returns to the fasting level more slowly than in normal individuals.^{4,5,6}

Because of this disagreement, we have availed ourselves of an opportunity to study the effect of hypothyroidism on carbohydrate metabolism under controlled conditions: we have measured the fasting serum sugar concentration, the blood sugar tolerance curve following ingested glucose, and the blood sugar changes following insulin injection in a group of non-diabetic patients before and after the development of the hypothyroid state, induced by total thyroidectomy⁷ performed for its therapeutic effect on chronic heart disease.⁸ In addition, these studies have been made on one patient who had diabetes and on one who, before operation, had mild hyperthyroidism as well as heart disease. In this note studies on the fasting serum sugar concentration and on the blood sugar curve following the ingestion of 100 gm. of glucose are reported. The second report of this series⁹ deals with the blood sugar changes following the subcutaneous administration of insulin before and after total thyroidectomy.

Methods of Investigation. Venous blood samples were utilized in the glucose tolerance studies. In 4 of 13 cases in which serum sugar measurements were made, arterial blood was utilized; in the remaining cases venous blood was employed. The serum and whole blood sugar measurements were made by the method of Folin and Wu,¹⁰ 5% sodium tungstate and $\frac{1}{3}$ normal sulphuric acid were used to precipitate the serum proteins. Urine sugar was estimated by the qualitative Benedict method. The basal metabolic rates were made in duplicate with a Collins-Benedict-Roth apparatus and calculated according to the Aub-Dubois normal standards.¹¹ Basal metabolic rate measurements were made on the same day or within a few days of the time when the blood was drawn for sugar analysis. The sugar tolerance test meal consisted of 100 gm. of glucose mixed with the juice of a lemon and dissolved in water up to 500 cc. Blood samples were collected before and one-half, one, two and three hours after ingestion of the glucose solution. Urine specimens were collected at each of these intervals if the patient was able to void.

The patients studied were operated on for the relief of long-standing congestive heart failure or of angina pectoris. The preoperative tests were made a few days before operation when the patients with congestive heart failure were edema-free and in condition suitable for operation; these patients were all edema-free and able to be up and about at the time of the postoperative tests. None of the patients with angina pectoris had suffered from an attack of anginal pain on the morning of the test. The diets of these patients were adequate in carbohydrate.

When tests were made one month or longer after operation clinical evidences of hyperthyroidism were manifest and the basal metabolic rates were usually between -20 and -30%. Some of the patients were receiving small doses of thyroid to prevent the development of untoward symptoms of myxedema, in accord with considerations outlined elsewhere.¹²

Results. Fasting Serum Sugar Concentration. Studies of the serum sugar before and at intervals up to 1 year after total thyroidectomy were made in 13 patients who showed no evidences of diabetes or thyrotoxicosis before operation (Table 1). Since a mild anemia develops in hypothyroidism, serum rather than whole blood was utilized for these studies, thus obliterating the effect of change in red cell volume on the sugar concentration. In 9 of the 13 cases the fasting serum sugar concentration decreased somewhat when hypothyroidism developed; at the sixth postoperative month the average decrease in these 9 cases was 12 mg. per 100 cc.; in 2 cases the serum sugar concentration did not change, and in the remaining 2 cases increased slightly (Table 1). Measurements in 3 patients (Cases 2, 3, and 4) (Table 1) as early as 2 weeks after operation revealed a slight decrease both in the fasting serum sugar and in the basal metabolic rate. All postoperative serum sugar concentrations were within the accepted normal limits.

TABLE 1.—FASTING SERUM SUGAR CONCENTRATIONS IN HUMAN HYPOTHYROIDISM FOLLOWING TOTAL ABLATION OF THE NORMAL THYROID GLAND.

Case	Age.	Preop. diagnosis.*	Serum sugar concentration—mg. per 100 cc.				
			Before operation.	2 wks.— 1 mo. postop.	6 mos. postop.	9 mos. postop.	1 yr. postop.
1. (E. W.)	27	C. H. F.	91	75	73		
2. (W. B.)	55	C. H. F.	93	87	79	...	89
3. (C. C.)	66	C. H. F.	90	71	75		
4. (A. B.)	57	A. P.	88	85	74		
5. (L. B.)	44	C. H. F.	96	..	84	87	82
6. (F. C.)	31	C. H. F.	68	..	92	83	77
7. (L. M.)	53	C. H. F.	107	..	99		
8. (W. D.)	22	C. H. F.	79	..	80	95	91
9. (B. Z.)	45	C. H. F.	94	..	84	101	100
10. (M. F.)	48	A. P.	92	..	92		
11. (E. P.)	58	A. P.	98	..	90		
12. (M. W.)	54	A. P.	91	..	117		
13. (M. C.)	57	A. P.	129	..	118		
Average B. M. R. % deviation from normal†			-5	-17	-30	-27	-26

* C. H. F. refers to congestive heart failure; A. P. to angina pectoris.

† Two patients (Nos. 3, 11) were given small doses of thyroid (Armour's) from the end of the first postoperative month, 6 other patients (Nos. 4, 5, 6, 8, 10, 13) received small doses of thyroid beginning with the 3d to 6th postoperative months.

Glucose Tolerance. Glucose tolerance tests were made before total thyroidectomy in 8 patients who showed no clinical evidence of diabetes or hyperthyroidism, and in the same patients at intervals after operation when conclusive clinical and laboratory evidences of hypothyroidism were present (Table 2). Thirteen glucose tolerance tests were made in 8 other patients only after total thyroidectomy (Table 3). In many of our cases the height and duration of the hyperglycemia following the ingestion of 100 gm. of glucose before operation were greater (Table 2; Fig. 1) than usually obtained in young normal individuals.^{13,14} Since our patients had heart dis-

ease and since many were above middle age (Table 2), this high normal type of glucose curve might be expected.¹⁴

TABLE 2.—AVERAGE RESULTS IN CASES IN WHICH TESTS WERE MADE AT POST-OPERATIVE INTERVALS ONLY.

No. of cases.	Age range.	Time of study.	B. M. R., % deviation from normal.	Serum sugar values following 100 gm. of glucose by mouth, mg. per 100 cc.					Urine sugar, gm.	Thyroid medication.
				Fast-ing.	Time after glucose.					
					30 min.	60 min.	120 min.	180 min.		
7	22-66	2-3 mos. postop.	-27	79	124	138	125	96	0	No thyroid in 6 cases; gr. $\frac{1}{5}$ daily in 1 case. Thyroid, gr. $\frac{1}{5}$ to $\frac{1}{3}$ daily in 2 cases. Thyroid, gr. $\frac{1}{5}$ daily in 1 case.
4	22-66	4-6 mos. postop.	-29	79	136	148	134	111	0	
2	22-66	10-13 mos. postop.	-27	88	135	121	107	92	0	

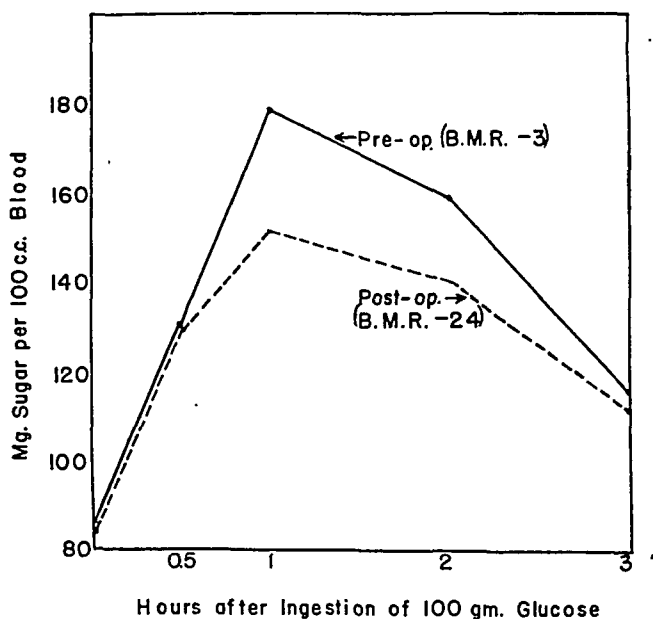


FIG. 1.—Average glucose tolerance curves before and after total thyroidectomy in a group of 7 patients, none of whom had evidence of diabetes or thyrotoxicosis prior to operation.

The glucose tolerance curves following total thyroidectomy were not strikingly different from those obtained before operation in the same subjects (Table 2); the only significant change in response to the glucose meal which may be attributable to the induced hypothyroidism was the somewhat low sugar concentration 1 and 2 hours after glucose, evident in 6 of 7 cases (Table 2; Fig. 1). In

Case 9 (Table 2) glucose (40 cc. of 50% solution) was administered intravenously; in this patient the maximum increments in blood sugar before and after operation were approximately the same, although the postoperative curve returned to the fasting level slightly sooner. In the 8 cases in whom glucose tolerance tests were made postoperatively only, the curves likewise revealed no abnormality.

Comparison of the glucose tolerance curves before and after total thyroidectomy in 1 diabetic patient (Case 9, Table 2), and in 1 hyperthyroid patient (Case 10, Table 2), both of whom had angina pectoris, revealed changes which were more striking than those found in the aforementioned group. In Case 9, a patient with frank diabetes controllable by diet, the glucose meal evoked a considerably lesser degree of hyperglycemia after the development of hypothyroidism (Table 2). In Case 10, a patient with mild hyperthyroidism and a decreased sugar tolerance, the response to ingested glucose was distinctly improved after hypothyroidism had been induced (Table 2). In these 2 cases, the glycosuria during the 3 hours following the glucose meal was considerably diminished after total thyroidectomy (Table 2).

Discussion. The effect of thyroid activity on carbohydrate metabolism in diabetic patients has been studied extensively. It is now well recognized that when hyperthyroidism develops in the course of diabetes, the diabetic condition is aggravated, whereas when myxedema develops in the course of diabetes, the diabetic condition may be benefited.^{15,16} The beneficial effect of lowering the basal metabolic rate in diabetic patients with hyperthyroidism is striking.^{15,16} Wilder and his associates¹⁷ have recently reported that a lowering of the basal metabolic rate from a normal to a sub-normal level by practically complete removal of the normal thyroid gland in a young diabetic patient was accompanied by an alleviation in the diabetic condition. Rudy, Blumgart and Berlin¹⁸ have likewise observed a beneficial effect from hypothyroidism induced by total ablation of the normal thyroid gland in a very severe diabetic patient. The alleviation of diabetes when hypothyroidism develops may be largely explicable on the basis of the lowered metabolic rate.^{15,19}

Whether hypothyroidism has an appreciable effect on the carbohydrate metabolism of non-diabetic patients has been unsettled, as pointed out above. The results of our investigation indicate that the development of hypothyroidism, following total thyroidectomy, has little effect on the carbohydrate tolerance and the fasting serum sugar level in those patients who have no evident abnormalities of thyroid or pancreatic function prior to operation. Although, after the development of hypothyroidism in this group of patients, the fasting serum sugar concentration and the hyperglycemia following glucose were usually slightly lower than preoperatively

(Tables 1 and 2), the changes seem too slight to be considered definitive in view of the normal intrinsic variability in the blood sugar.

In the patient with diabetes but no thyroid disease (Case 10, Table 2), on the other hand, hypothyroidism induced by total thyroidectomy appeared to increase the carbohydrate tolerance considerably. This is in accord with the clinical observations that when myxedema, spontaneous or induced, develops in the course of diabetes, the diabetic condition may be benefited.^{14,17,18} Similarly, in Case 11 (Table 2), a patient with hyperthyroidism and an abnormal glucose tolerance curve before operation, the glucose curve became more nearly normal when hypothyroidism developed. It would appear from our results that if the carbohydrate metabolism is deranged, the development of hypothyroidism has a beneficial effect, whereas if the carbohydrate metabolism is normal, the development of hypothyroidism has no or very little influence upon it. This observation finds a counterpart in the observation of Andersen¹⁶ that if the glucose tolerance in patients with exophthalmic goiter is markedly decreased, subtotal thyroidectomy causes a return toward normal, whereas in those hyperthyroid patients who before operation have a normal carbohydrate metabolism, subtotal thyroidectomy exerts no definite influence.

Summary. 1. The fasting serum sugar concentration was found normal in non-diabetic patients with hypothyroidism induced by total thyroidectomy. The postoperative sugar values tended to be slightly lower than those obtained before total thyroidectomy.

2. The glucose tolerance was normal in non-diabetic patients with induced hypothyroidism. The hyperglycemia produced by the glucose was usually slightly less after total thyroidectomy than preoperatively.

3. One diabetic patient and one patient with hyperthyroidism showed abnormal rises in blood sugar following glucose ingestion before operation; after hypothyroidism was induced, both of these patients showed marked decreases in the degree of hyperglycemia following glucose.

4. Our findings indicate that the carbohydrate metabolism is not significantly influenced by hypothyroidism induced by total thyroidectomy except when a derangement of carbohydrate metabolism is evident prior to operation.

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CARBOHYDRATE METABOLISM IN HUMAN HYPOTHYROIDISM INDUCED BY TOTAL ABLATION OF THE THYROID GLAND.

II. THE BLOOD SUGAR RESPONSE TO INSULIN.*

BY MAURICE I. ABRAMS, M.D.,

ASSISTANT IN MEDICINE, HARVARD MEDICAL SCHOOL,

AND

D. ROURKE GILLIGAN, M.S.,

RESEARCH FELLOW IN MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

(From the Medical Research Laboratories of the Beth Israel Hospital, and the Department of Medicine, Harvard University Medical School.)

In the preceding article¹ we have reported that the fasting serum sugar concentrations and the glucose tolerance curves are normal in non-diabetic patients with hypothyroidism induced by total ablation of the thyroid gland. As compared with the values observed before thyroidectomy, the fasting serum sugar concentration tended to be slightly decreased and the glucose tolerance tended to be slightly increased after hypothyroidism had developed.¹

We have been unable to find any studies in the literature concerning the influence of hypothyroidism upon sensitivity to insulin in man; on the other hand, experimentation both in diabetic and non-diabetic animals has resulted in the opinions that the sensitivity to insulin after removal of the thyroid gland is either increased^{2,3} or unchanged.⁴ In this paper we report the blood sugar response of non-diabetic patients to the subcutaneous injection of 20 units of insulin before and after the development of hypothyroidism induced by total ablation of the thyroid gland. It has been possible to follow closely the development and extent of the hypothyroid state by observations of the clinical picture, the basal metabolic rate, the serum cholesterol concentration and other related measurements.⁵

* This investigation was aided by a grant from the William W. Wellington Memorial Research Fund of Harvard University.

Methods. The subjects of this study were patients with chronic intractable heart disease who, before total thyroidectomy, showed no evidences of diabetes or hyperthyroidism. Total ablation of the thyroid glands was performed for its beneficial effect on congestive heart failure or angina pectoris, in accord with the considerations of Blumgart and his associates.⁶ None of the patients was particularly malnourished and each of them received a diet adequate in carbohydrate for several weeks before the response to insulin was studied. The ages varied from 22 to 58 years.

Total thyroidectomy was performed according to the technique of Berlin⁷ and hypothyroidism developed in every instance. The blood sugar concentration was measured by the method of Folin and Wu.⁸ Basal metabolic rate measurements were made the same day or within a few days of the insulin studies; the measurements were made in duplicate with a Collins Benedict-Roth apparatus and calculated according to the Aub-DuBois normal standards.⁹ After obtaining a sample of venous blood from the patient in the postabsorptive state, 20 units of insulin (Lilly) was injected subcutaneously and samples of venous blood were drawn $\frac{1}{2}$, 1, 1 $\frac{1}{2}$, and, at times, 2 hours after the injection. In each patient the blood pressure, pulse and general appearance were watched closely for the development of signs of insulin reaction. In several instances the experiment was terminated after 1 $\frac{1}{2}$ hours because the patient was distressed. At the termination of each test the patient was given 500 cc. of orange or pineapple juice.

Results and Discussion. The blood sugar response to 20 units of insulin injected subcutaneously was measured in 6 subjects before, and at intervals after total ablation of the thyroid gland. In 7 additional patients studies were made only after hypothyroidism had developed. The blood sugar changes following insulin, together with the basal metabolic rate values, are given in Table 1. At the time of the earliest post-operative measurements, made from 2 or 3 weeks after operation, the basal metabolic rates had shown characteristic decreases (Table 1), but the clinical picture of hypothyroidism was not present. When tests were performed from one month to 1 year after operation, clinical evidences of hypothyroidism, varying from mild signs and symptoms to marked myxedema, were manifest, the basal metabolic rates were low (Table 1) and the serum cholesterol concentrations, measured in several cases, were elevated.

In the 6 patients studied before and after operation, the post-operative blood sugar response to insulin, regardless of the degree of hypothyroidism present, was essentially the same as that obtained before operation. The average maximum decrease in blood sugar following the subcutaneous injection of 20 units of insulin in these 6 patients before operation was 34%; the average maximum decrease in these same patients after the development of hypothyroidism was likewise 34%. The average basal metabolic rate before operation was -3% and after operation was -22%.

The blood sugar response to insulin in the 7 patients studied only postoperatively showed no correlation with the degree of hypothyroidism and was similar to that observed both before and after operation in the previous group of patients. The average maxi-

imum decrease in blood sugar in these 7 patients was also 34%; the average basal metabolic rate was -25% (Table 1).

TABLE 1.—HUMAN TOLERANCE TO INSULIN IN HYPOTHYROIDISM, INDUCED BY TOTAL THYROIDECTOMY.

Case No.	Age.	Pre-operative diagnosis.*	Time of study.	Basal metabolic rate (deviation from average normal), %.	Blood sugar changes with 20 units insulin.				Maximum blood sugar decrease, %.
					Fasting (before insulin), mg. per 100 cc.	Time after insulin.			
						60 minutes, mg. per 100 cc.	90 minutes, mg. per 100 cc.	120 minutes, mg. per 100 cc.	
1	42	A. P.	Before op.	- 7	81	52	..	52	35
			3 wks. post-op.	-29	80	61	..	50	37
2	41	A. P.	Before op.	+ 8	85	56	54	50	40
			3 wks. post-op.	-15	83	54	54	..	40
3	45	C. H. F.	Before op.	- 6	117	95	70	70	40
			4 wks. post-op.	-24	90	67	66	..	26
4	45	C. H. F.	Before op.	+ 9	100	83	74	..	26
			3 wks. post-op.	-20	96	84	74	74	23
			6 wks. post-op.	-24	102	66	64	64	37
5	36	C. H. F.	Before op.	-14	75	61	..	54	28
			2 wks. post-op.	-17	78	62	65	54	31
			5 wks. post-op.	-21	75	66	54	59	28
6	58	C. H. F., A. P.	Before op.	- 7	100	69	67	..	33
			3 wks. post-op.	-16	76	62	54	50	34
7	31	C. H. F.	8 wks. post-op.	-11	75	55	57	..	24
8	22	C. H. F.	5 mos. post-op.	-19†	80	71	..	50	37
9	18	C. H. F.	4 mos. post-op.	-36	85	80	68	60	23
10	46	A. P.	4 wks. post-op.	-20	91	80	65	..	28
11	52	A. P.	2 wks. post-op.	-24	95	72	61	..	35
			4 mos. post-op.	-40	95	80	67	64	33
12	34	C. H. F.	4 wks. post-op.	-35	85	54	49	..	42
			3 mos. post-op.	-31	91	83	49	..	46
13	42	C. H. F.	1 yr. post-op.	-16	95	54	51	..	46
14	51	A. P., H., D.	Before op.	+20	100	95	72	70	30
			2 wks. post-op.	-18	87	59	53	..	27
			4 wks. post-op.	-33	114	58	61	58	50

* A. P. signifies angina pectoris; C. H. F., congestive heart failure; H., mild hyperthyroidism, and D., mild diabetes.

† This patient was receiving small doses of thyroid ($\frac{1}{3}$ grain daily, Armour's) to obviate untoward symptoms of myxedema.

The blood sugar response to insulin was also studied before and after total ablation of the thyroid gland in 1 patient with mild diabetes and mild hyperthyroidism (Case 14, Table 1). Before operation, when the basal metabolic rate was +20, the maximum decrease in blood sugar following the injection of 20 units of insulin, was 30%; after operation, when the basal metabolic rate was -33%, the maximum decrease was 50%. In view of the range of maximum

blood sugar decreases after insulin observed by us in our other patients (Table 1) and by others ^{10,11} neither the pre-operative nor the post-operative decrease in this patient can be considered abnormal.

The lowest blood sugar values obtained after the injection of 20 units of insulin varied from 49 to 70 mg. per 100 cc. of blood. At these concentrations of blood sugar, approximately one-half of the patients showed some characteristic signs and symptoms of hyperinsulinism. The earliest symptoms usually were weakness and a sensation of being "light-headed." Hunger and thirst were rarely found, even though each patient was questioned closely concerning these symptoms. The heart rate and the blood pressure showed no appreciable changes, probably because the amount of insulin used was insufficient to induce marked reactions.¹² The patients with moderate to marked hypothyroidism showed the same signs and symptoms of hyperinsulinism at approximately the same level of blood sugar as did the patients before total thyroidectomy, when the basal metabolism was normal.

The average maximum decrease in blood sugar following the injection of 20 units of insulin in our patients coincides with the average maximum decrease in blood sugar observed by Fletcher and Campbell¹⁰ following the injection of the same amount of insulin in 5 normal individuals.

The above observations, showing that the development of hypothyroidism does not increase sensitivity to insulin in man, differ from the results of several investigators who found that insulin sensitivity in rabbits was increased many fold after thyroidectomy.^{3,13} Studies in thyroidectomized animals are at times difficult to interpret because of the inability to maintain and evaluate the degree of hypothyroidism. Total ablation of the thyroid gland in human subjects, however, causes persistent hypothyroidism⁷ which can be evaluated satisfactorily by basal metabolic rate and serum cholesterol measurements, and by clinical observations.

It has been quite definitely established that there is essentially no ability to counteract the effect of insulin in adrenalectomized and in sympathectomized animals.^{14,15} The finding of a normal blood sugar decrease following insulin in our patients after total thyroidectomy indicates that the response of the sympathetico-adrenal system to insulin in these patients with hypothyroidism is normal. Furthermore, our results indicate that there is no antagonism between the internal secretions of the normal thyroid gland and that of the pancreas. The favorable influence of hypothyroidism upon diabetes^{16,17,18} would appear, therefore, to be related to other factors in carbohydrate metabolism.

Summary. 1. The sensitivity to insulin has been observed in non-diabetic, non-hyperthyroid patients before and after the development of hypothyroidism induced by total ablation of the thyroid gland.

2. In these patients no appreciable difference has been found in the average maximum decrease of blood sugar following the subcutaneous injection of 20 units of insulin before and after hypothyroidism developed. The average decrease in blood sugar in all studies following the injection of 20 units of insulin was 34%.

3. Signs and symptoms of mild hyperinsulinism were manifest in patients with hypothyroidism at the same level of blood sugar as in patients with normal metabolic rates.

4. Our results indicate that the response of the sympathico-adrenal system to insulin is normal in these patients with hypothyroidism, and that there is no antagonism between the internal secretions of the normal thyroid gland and of the pancreas.

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MULTIPLE PARATHYROID TUMORS WITH MASSIVE MEDIASTINAL AND SUBCUTANEOUS HEMORRHAGE.

A CASE REPORT.

By RICHARD B. CAPPS, M.D.,

ASSISTANT RESIDENT, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL;
RESEARCH FELLOW IN MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services [Harvard], Boston City Hospital, and the Department of Medicine, Harvard Medical School.)

IN the past few years parathyroid tumors, with the characteristic manifestations that usually accompany them, have become a well-established clinical entity. Until recently, however, no distinction

has been drawn between cases of single and multiple parathyroid enlargement. Albright, Bloomberg, Castleman and Churchill¹ have now shown that the histologic appearance of the two types is quite different and have suggested that the two types may be etiologically distinct. In the multiple enlargement type the tumor cells are uniformly of the large, clear ("wasserhell") variety; while the histologic picture of the single tumor case presents a diversity of cell types and cell sizes. At present, there is no satisfactory clinical method of distinguishing between these two groups.

Because examples in the literature of multiple parathyroid tumors are rare and because of the extremely unusual clinical picture presented, it seems of value to report the following case:

Case Report. A 50-year-old white, married, male, Lithuanian textile worker entered the hospital on October 3, 1933, because of a "sore throat" with progressive swelling of his neck of 4 days' duration. On account of language difficulties the *history* obtained was scanty and unreliable.

Previous to the present complaint the patient had apparently been well except for some progressive weakness during the 5 weeks before admission. For a week preceding the onset of his "sore throat" he had been on a heavy drinking spree which was terminated by a short attack of delirium tremens.

Four days before admission he developed a sore throat without fever, accompanied by a diffuse, painless swelling of the neck. As the swelling gradually became worse he noticed increasing difficulty in swallowing, as well as in breathing and talking. He had a slight cough productive of small amounts of yellow sputum. Occasionally there were mild headaches and spells of dizziness.

The day before admission he noticed a large "bruised" area on the anterior aspect of the right chest and neck. No history of trauma could be obtained. On admission the swelling had extended to his face and he was able to take only fluids by mouth, and these with difficulty.

The *family history* was irrelevant. The patient had for years drunk an excess of alcohol. The *past history* revealed that he had frequent colds and sore throats following his alcoholic sprees. Recently there had been slight dyspnea on exertion.

The *physical examination* revealed a well-developed and rather obese middle-aged man who was sitting up in bed acutely ill. He was in moderate respiratory distress and was very nervous, complaining frequently of double vision. The skin of the face and neck was of an unusual reddish-blue color, as if congested. There was slight edema of the face and cyanosis of the lips; the conjunctivæ were moderately injected; the tonsils were markedly enlarged but there was no exudate. The entire pharynx, soft palate and tonsillar region were of a reddish-purple color due to multiple minute hemorrhages and to congestion with blood. In the retropharyngeal region was a marked swelling which appeared to be due to a large hematoma.

The neck, especially the anterior aspect, was diffusely and markedly enlarged. Palpation revealed no lymph-node enlargement or masses except for an indefinite firmness in the midline, extending beneath the manubrium. There was only slight tenderness and slight pitting. No abnormal pulsation, no bruit, nor any evidence of collateral circulation was made out.

Over the anterior aspect of the right chest extending down to the nipple was a large ecchymotic area which pitted moderately on pressure (Fig. 1). Percussion showed definitely increased retromanubrial dullness, especially to the right, and also dullness posteriorly over both lung apices, extending 2 to 3 inches below the scapular spines. Decreased breath sounds with

some bronchial breathing were heard over these latter areas but no râles were detected. Tactile fremitus was diminished. The remainder of the lung was clear. There was no apparent cardiac enlargement. The heart sounds were distant but of good quality and there were no murmurs. The pulse rate was 84 per minute and regular. Blood pressure in the right arm was 140 mm. Hg systolic and 96 diastolic, while in the left the systolic was 160 and the diastolic 110. Abdominal examination was negative except that the liver was palpable for 3 cm. below the costal border.



FIG. 1.—Appearance of the patient on admission. Note the discoloration of the face, swelling of the neck, and the large ecchymosis on the chest.

Laboratory Examinations. Red cell count, 4,790,000; hemoglobin, 12.64 grams per 100 cc. A blood smear showed the red cells to be normal. The white count was 11,600 (68% neutrophils, 16% lymphocytes and 16% monocytes). The platelets, bleeding time and the clotting time of the blood were all found to be normal.

Four urine specimens and one stool were normal. The sputum contained no blood or acid-fast organisms. Roentgen ray examination of the chest was interpreted as showing "a rounded tumor mass in the superior mediastinum and rising above the clavicles" (Fig. 2). This picture was thought to be consistent with aneurysm or some other mediastinal tumor.

The patient's course in the hospital was one of progressive decline. His temperature varied between 97° and 99° F.; respirations between 15 and 25 per minute. Because of extreme restlessness he was given sedatives freely. His general condition, however, gradually became worse and his breathing became extremely labored. Finally, on the 4th day following admission, he developed delirium tremens, his pulse became thready and he died shortly thereafter.

The clinical diagnosis was mediastinal tumor, with hemorrhage into the

tumor and subcutaneous tissues. The tumor was thought to be either a neoplasm or an aneurysm. *Necropsy* (performed 10 hours postmortem by Dr. Soma Weiss): *Grossly*, the body showed only what was noted on physical examination. On making an incision over the thorax, blood was found to ooze diffusely from the tissues. All the anterior thoracic muscles and the anterior mediastinum around the base of the heart were infiltrated with blood. The pericardium and heart were normal, except for slight mitral thickening. The aorta was soft and elastic, and was without lesions of any kind. The lungs showed slight basal congestion.

On each side of the trachea at the level of the clavicle a nodule was found. The larger one on the right measured 7.0 by 3.5 by 2.1 cm. and weighed 22 grams. It was ovoid in shape, fluctuant and well encapsulated. On incision it was found to be filled with blood which could be seen dissecting the tumor tissue through the capsule. From this point, blood could be traced to all the subcutaneous and mediastinal hemorrhagic areas. The cut surface of the nodule was pale brownish-gray with many hemorrhagic areas of varying size. The tissue was of a very soft consistency. The mass on the left side was smaller, weighing 13.6 grams and measuring 2.4 by 3.5 by 2.1 cm. In shape and appearance and on section it was exactly similar to the other tumor except for the absence of hemorrhage.

The thyroid was not remarkable. No normal parathyroids were seen grossly. The liver (wt. 2200 gm.) was rather soft and friable, and light yellow in color on cross section. The intestines, adrenals, kidneys, spleen and pancreas were all essentially normal.

Anatomical diagnosis: parathyroid adenomata (made from frozen sections), hemorrhage into one tumor with suffusion of mediastinal tissues and muscles of the neck and thorax, fatty infiltration of the liver, and slight mitral valvulitis.

The *histologic examination* of the heart, pancreas, adrenals and testes was essentially negative. The lungs and spleen showed congestion. In many organs were seen occasional clumps of orange-yellow pigment giving a positive test for iron. Most of the liver cells were vacuolated and in the cytoplasm of a few of the periportal liver cells irregular, red-staining masses were visible.

The renal tubules were moderately distended and contained coagulated albumin. In the cortex, the tubular epithelium presented swollen, clear cytoplasm. Throughout, small patches of sclerosis were also seen. Sections of bone from the vertebral bodies, the ilium and the femur failed to disclose any abnormality.

The appearance of the tissue from both parathyroid tumors was essentially the same (Fig. 3). Masses of medium-sized cells were found with rather clear cytoplasm, small round or oval dark-staining nuclei, and well-defined cell margins separated by fine connective-tissue trabeculations. For the most part, the cells were loosely arranged and frequently occurred in cord-like masses. There were areas of hemorrhage and rare small islands of fat tissue. Capillary bloodvessels were numerous and occasional clumps of orange-yellow pigment were found. There were rare cyst-like spaces filled with a homogeneous pink-to-bluish staining material. No mitotic figures were detected. The absence of fat in the large clear cells was demonstrated by the fact that they did not stain with Scharlach R. In the same cells Best's carmine stain revealed small droplets of glycogen. The capsule was well defined and partly covered with an organizing blood clot. In the tissues of the neck a small parathyroid gland was discovered during the microscopic examination. The cells were all of the same large, clear type as those composing the two tumors.

The supplementary microscopic diagnoses were hyperplasia of the parathyroids, alcoholic cirrhosis and hemosiderosis of the spleen, liver, adrenals and bone marrow.

Comment. From a diagnostic standpoint this patient presented on admission a most unusual and interesting picture. Clinically, the involvement of the face and neck with diffuse cutaneous hemorrhage and swelling, accompanied by dysphagia and dyspnea, seemed best explained by assuming the presence of both a large infiltrating hemorrhage and a superior mediastinal obstruction. Roentgen ray and physical examination suggested the presence of a superior mediastinal mass which was obviously causing the obstruction and was probably the source of the hemorrhage. The true nature of the tumor was not recognized even at autopsy until frozen sections had been examined. It should be mentioned in passing that a somewhat similar appearance of the head and neck is seen in two conditions besides an actual hemorrhage, namely, so-called "traumatic cyanosis,"^{2,3} and rupture of a mediastinal aortic aneurysm into the superior vena cava.⁴

Massive subcutaneous and interstitial hemorrhage from a parathyroid tumor such as occurred in this case has not been previously reported in the literature. Petechial hemorrhages into the parathyroid glands are occasionally seen in infants with tetany,^{5,6} but in such cases the bleeding occurs under quite different circumstances from that of the patient under discussion, and so is not comparable.

Histologically both tumors were almost identical with those reported by Albright and his coworkers.¹ It should be noted that the normal-sized parathyroid gland, recognized only on microscopic examination of the tissues of the neck, was found to have a histologic appearance similar to that of the tumors themselves. As no other parathyroids were discovered in spite of a careful search, it must be concluded that all of this patient's parathyroid tissue was in the same abnormal state.

In the absence of chemical blood studies no definite conclusions can be drawn in regard to the state of the calcium and phosphorus metabolism. Postmortem Roentgen rays of the entire skeleton, however, as well as histologic examination of several bones, revealed no decalcification or cysts. The postmortem bladder urine contained 3.18 mg. per 100 cc. of calcium and 0.506 mg. per 100 cc. of phosphorus,* and had a specific gravity of 1.030. Although these figures are essentially normal,^{7,8,9} the urine was obtained under such uncontrolled conditions that the results are only moderately significant. Thus in this case we have no evidence of hyperfunction of the parathyroids; but because it has been shown^{10,11} that even with normal kidneys bone changes are not necessarily present, it is impossible to state that in this case there was no hyperparathyroidism.

Summary. A case is reported of multiple parathyroid tumors with massive mediastinal and subcutaneous hemorrhage arising spontaneously from one—a complication not previously recorded. The patient had no symptoms or signs of hyperparathyroidism but

* Analyses kindly performed by Dr. F. Albright.

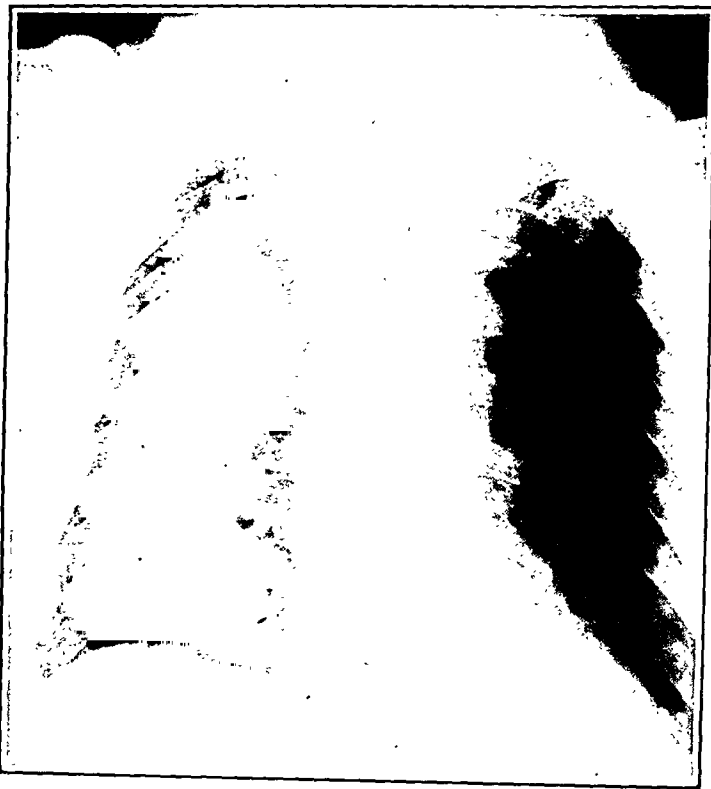


FIG. 2.—Roentgenogram of the thorax. Note the bilateral superior mediastinal masses.

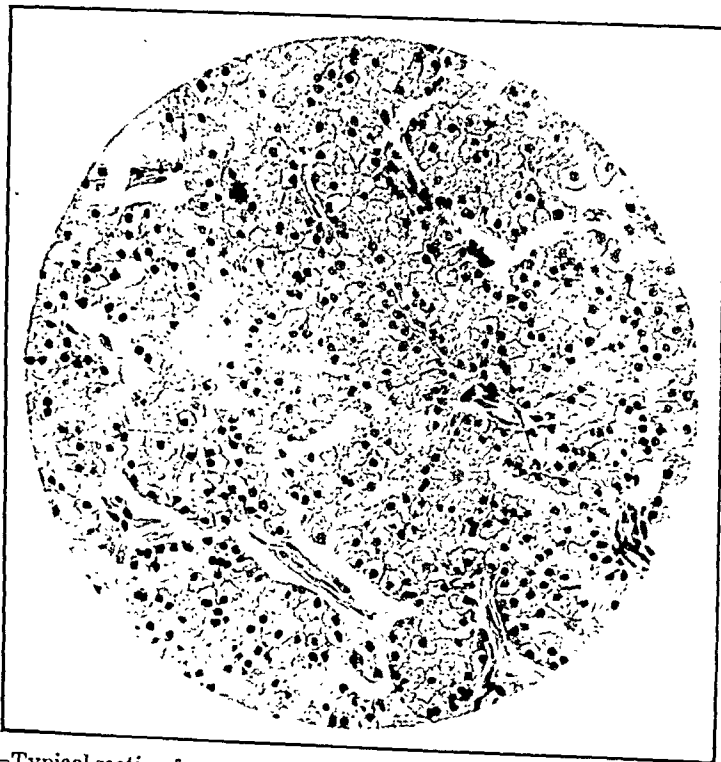
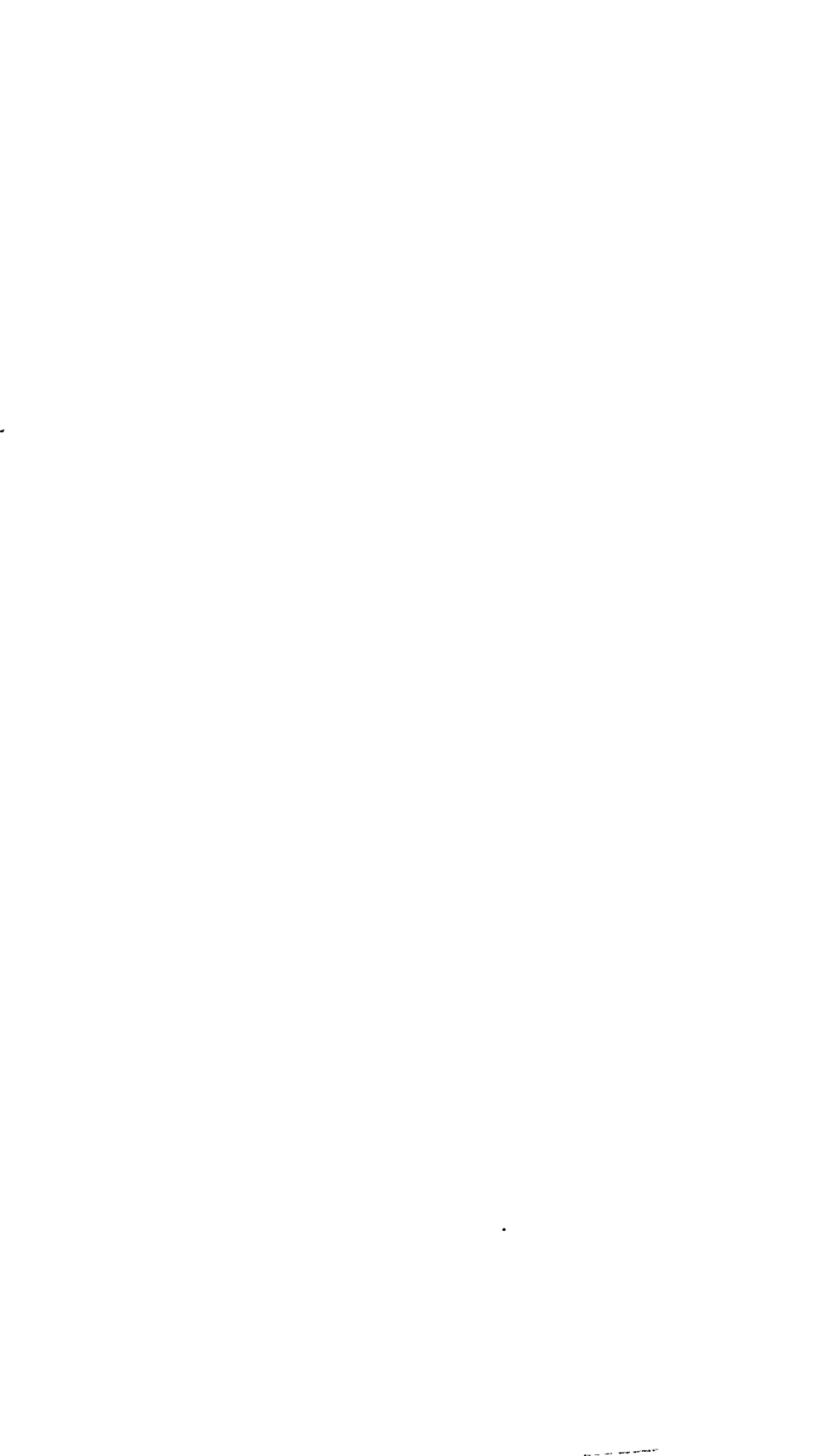


FIG. 3.—Typical section from one of the parathyroid tumors. Note the uniform type of large clear cell, and the tendency to gland formation.



no calcium or phosphorus determinations on the blood were made. His complaints were entirely related to the hemorrhage. All the parathyroid tissue examined proved to be histologically identical with that of the cases of multiple parathyroid tumor recently reported by Albright and his coworkers.

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THE CAUSES OF COMA IN PATIENTS ENTERING A GENERAL HOSPITAL.*

BY PHILIP SOLOMON, M.D.,

AND

CHARLES D. ARING, M.D.,

BOSTON, MASS.

(From the Neurological Unit, Boston City Hospital, and the Department of Neuropathology, Harvard Medical School.)

THE great frequency with which patients are brought to a general hospital in coma is not fully appreciated. There were 37,438 entries in this hospital in the year 1933. (These do not include entries to the South Department for contagious diseases.) Of these, 1167, approximately 3%, entered in coma. These figures are startling and obviously do not apply to all hospitals, for city hospitals doubtless receive a higher proportion of patients in coma than do other hospitals. The present paper is concerned with the relative frequency of the various causes of coma as a presenting sign as an aid to accurate diagnosis and immediate treatment. The records of all patients who entered this hospital in 1933 were examined† and those in which coma was mentioned as a presenting sign were analyzed. Many of these patients, including all with a doubtful diagnosis, were personally seen by one or the other of the authors in their capacity as neurologic consultant.

* The authors wish to express their appreciation of Dr. Stanley Cobb's invaluable advice and assistance in the course of this work.

† We wish to express our indebtedness to Mary S. Aring for her diligence in carrying out this part of the work.

Among the various causes of coma there are some which require emergency treatment to save life, for example, diabetes, hyperinsulinism, poisoning, traumatic shock, exsanguination, subdural hematoma, brain tumor, meningitis and eclampsia. The importance of immediate diagnosis when the coma is of unknown origin is evident. Making diagnosis more difficult is the fact that patients in coma frequently enter the hospital without a history (68% of the authors' 1167 cases).

A knowledge of the more common causes of coma as a presenting sign, and the relative frequency of these causes, would obviously be helpful in making the diagnosis. The literature contains very little statistical data of this sort. Camauer¹ published an analysis of 26 cases, of which 8 proved to be cerebral hemorrhage, 5 uremia, 3 trauma, 2 eclampsia, 2 cardiac insufficiency, 1 endarteritis obliterans luetica, 1 cerebral neoplasm, 1 thrombosis, 3 unknown causes. Bissell and Le Count² analyzed the cause of death in 400 cases of patients who died in coma, and Holcomb³ continued this analysis with 346 more cases. Because only 22.5% of the 1167 cases of our series ended fatally, and because many cases develop coma in the hospital as a terminal state, Bissell and Le Count's and Holcomb's statistics are not applicable to the problem of coma as a presenting sign. The textbooks are of little assistance. They mention many causes of coma and discuss at length some that are rare, while others that are more common they do not include at all. They do not attempt to give any idea of the relative frequency of the various causes.

TABLE 1.—CAUSES OF COMA AS A PRESENTING SIGN AND THEIR MORTALITY.

Disease.	Number of cases.	Per cent total comas.	Per cent non-alcoholic comas.	Cases of group ending fatally.	Per cent of group ending fatally.
Alcohol	690	59.1	..	14	2.0
Trauma	152	13.0	32.0	48	31.5
Cerebral vascular lesions	118	10.1	24.7	91	77.1
Poisoning	33	2.8	7.0	3	9.0
Epilepsy	28	2.4	6.0	0	0.0
Diabetes	20	1.7	4.2	11	55.0
Meningitis	20	1.7	4.2	20	100.0
Pneumonia	20	1.7	4.2	18	90.0
Cardiac decompensation	17	1.4	3.5	12	70.6
Exsanguination	10	0.9	2.1	10	100.0
Central nervous system					
syphilis	7	0.6	1.4	0	0
Uremia	7	0.6	1.4	7	100.0
Eclampsia	7	0.6	1.4	3	42.8
Miscellaneous	38	3.2	8.0	26	68.4
Total	1167	100.0	100.0	263	22.5%

The 1167 cases discussed below represent unselected serial cases entering the hospital with coma as a presenting sign. Table 1

gives the various causes of coma in these cases. Fig. 1 illustrates the relative frequency of these causes.

Alcoholism (690 cases, 59.1% of total cases of coma; mortality in this group, 2%). The proportion of alcoholics entering the Boston City Hospital is undoubtedly greater than the proportion entering the average hospital, because "drunks" from all parts of the city are brought here. Most of the records of alcoholic patients are inadequate. The data gathered on alcoholic coma are, therefore, subject to error. There were 2079 admissions for alcoholism in the year 1933 (6% of the total admissions). The records of 690 of these (33%) mentioned coma as a presenting sign. Many of these comatose alcoholics also had injuries. There were minor head injuries in 80; minor injuries elsewhere on the body in 16

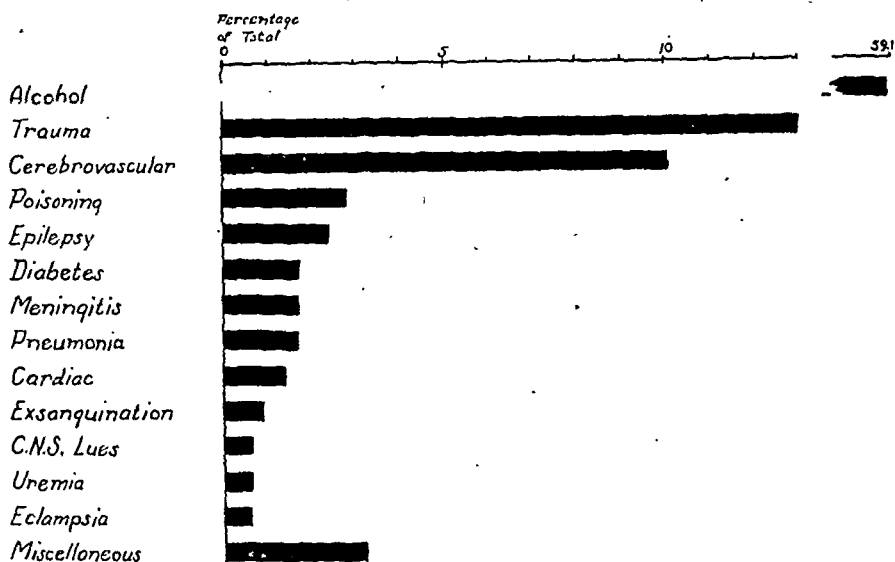


FIG. 1.—Causes of coma on admission to the hospital, 1167 cases.

In these cases coma was listed as being of alcoholic origin, although it is possible that injury played some part in its causation. Where alcoholism was associated with severe head injury, such as a fractured skull, contused or lacerated brain, or extradural or subdural hemorrhage, the coma is listed under head injuries and alcohol is considered as a secondary factor. Alcohol was a secondary factor in 26 cases of severe head injury and in 6 cases with other causes of coma; 62% of all the coma cases had alcoholism as either a primary or a secondary factor.

Trauma (152 cases, 13% of total cases of coma; mortality in this group, 31.5%). Among the traumatic comas, injuries to the head were by far the most common cause (Table 2). In a few cases, injuries to the chest, pelvis or spinal cord produced coma. Among the head injuries there was a relatively high proportion of subdural

and extradural hemorrhages. The other head injuries have been classified according to the extent of injury to the brain (Munro⁴) as judged by the period of unconsciousness, the character of the spinal fluid, other physical findings, such as bleeding from the ear, the subsequent course in the hospital and in some cases by postmortem findings. The high proportion of severe brain injuries and of skull fractures is understandable, since the cases here considered are head injuries that enter the hospital in coma.

TABLE 2.—COMA DUE TO TRAUMA.

Type.	Number of cases.	Per cent of total head injuries.	Cases with fractured skull.	Per cent with fractured skull.
Concussion	17	12	0	0
Edema of brain	20	15	3	15
Contusion of brain	38	28	9	24
Lacerated brain	47	34	41	87
Subdural hemorrhage	12	8	4	33
Extradural hemorrhage	3	3	2	67
Total head injuries	137	100	59	43
Chest injury	7			
Pelvis injury	4			
Spinal cord injury	4			
Total	152			

TABLE 3.—COMA DUE TO CEREBRAL VASCULAR LESIONS.

Type.	Number of cases.	Per cent of cerebral vascular lesions.
Hemorrhage	49	42
Thrombosis	29	25
Hypertensive and arteriosclerotic encephalopathy	10	8
Embolus	5	4
Primary subarachnoid hemorrhage	4	3
Undetermined	21	18
Total	118	100

Cerebral vascular lesions (118 cases, 10.1% of total coma cases; mortality in this group, 77.1%). After alcoholism and trauma, cerebral vascular lesions are by far the most common cause of coma as a presenting sign (24.7% of the non-alcoholic group). In analyzing the types of cerebral vascular lesions (Table 3), we find that cerebral hemorrhage is most common. We have not accepted this diagnosis unless the history and physical findings were corroborated either by autopsy evidence or the presence of gross blood in the spinal fluid. There is reason to suppose (Merritt and Aring⁵) that in cerebral vascular lesions with or without coma, cerebral thrombosis is more common than cerebral hemorrhage. The presence of coma as a presenting sign favors the diagnosis of hemorrhage as against thrombosis, while the absence of coma is in favor of thrombosis. There were 4 cases of cerebral emboli, and 4 of pri-

mary subarachnoid hemorrhage. In 21 of our cases where the diagnosis of cerebral vascular injury was quite clear because of the history and physical findings, there was not sufficient evidence to determine the type of injury. In 10 cases the diagnosis of encephalopathy on the basis of hypertension, arteriosclerosis, or both, was made clinically. The so-called "cerebral vascular spasms" would fall into this group.

Poisoning (33 cases, 2.8% of total cases of coma; mortality in this group, 9%). Acute poisoning (non-alcoholic) was the fourth most common cause of coma in this series. Of 33 cases, 16 were caused by barbitol or its derivatives, 12 by carbon monoxid, 1 each by bromid, permanganate, nitrobenzin, lysol and sodium nitrate. The patient who took lysol died, as did also the patient who took nitrobenzin and one who took barbitol.

Epilepsy (28 cases, 2.4% of total cases of coma; mortality, 0). This number of patients entering the hospital in coma following an epileptic seizure is probably not unusual for a city hospital. Of the 28 cases recorded here, 2 represent the same patient on different entries. Several of the others had been admitted in the same condition in previous years.

Diabetes (20 cases, 1.7% of total cases of coma; mortality in this group, 55%). Diabetic coma is not yet rare. Of the 20 cases in our series, 3 represent the same patient on different admissions. All but 7 of these cases were known diabetics, in whom the coma was precipitated by infections or indiscretions in diet. There were 3 with acute upper respiratory infection, 3 with bronchopneumonia, 2 with abscesses, 2 with gangrene of the foot, 1 with an infected bed sore and 2 had overstepped dietary limitations. Of the remaining 7 cases, 1 had an acute suppurative parotitis; the others were uncomplicated.

Meningitis (20 cases, 1.7% of total cases of coma; mortality in this group, 100%). It is not generally realized that meningitis is as common a cause of coma as diabetes among hospital entrants. Of the cases reported here, the organism was the pneumococcus in 9, the tubercle bacillus in 4, the meningococcus in 2, the streptococcus in 2, the staphylococcus in 1 and the organism was not identified in 2.

Pneumonia (20 cases, 1.7% of total cases of coma; mortality in this group, 90%). Pneumonia is not mentioned in the textbooks as one of the diagnoses to be considered in cases in which coma is a presenting sign. Yet pneumonia is 3 times as common as uremia in our series. Of our 20 cases, 13 were bronchopneumonia and 7 were lobar pneumonia. Ten of the 18 fatal cases died within 24 hours after admission.

Cardiac decompensation (17 cases, 1.4% of total cases of coma; mortality in this group, 70.6%). There were 17 patients of the total group studied who entered the hospital in coma because of

cardiac decompensation. This cause of coma is also little appreciated. As in the pneumonia comas, many of these patients were moribund; 8 of the 12 fatal cases died within 24 hours after admission. Coronary thrombosis was the cause of the attack in 5 cases, 2 had rheumatic, 1 hypertensive and 9 arteriosclerotic heart disease.

Exsanguination (10 cases, 0.9% of total cases of coma; mortality in this group, 100%). In 4 of these cases the bleeding was due to injury, the hemorrhage being external in 2 and internal in 2. Of the remaining 6 cases, in 2 the bleeding was due to rupture of an esophageal varix in conjunction with cirrhosis of the liver, in 2 to carcinomatous erosion in the gastro-intestinal tract, in 1 to the rupture of an aortic aneurysm, and in 1 to a tuberculous hemoptysis.

Central Nervous System Syphilis (7 cases, 0.6% of total cases of coma; mortality, 0). In the cases of coma due to syphilis of the central nervous system, all had had repeated attacks of unconsciousness, usually with convulsions. In 3 there was evidence of parenchymatous involvement, and the diagnosis of dementia paralytica was made.

Uremia (7 cases, 0.6% of total cases of coma; mortality in this group, 100%). The relatively few cases of uremia in our series surprised us. Many more patients develop uremic coma terminally while on the wards. It would seem that kidney insufficiency in most instances is gradual enough in onset and produces enough symptoms to bring the patient to the hospital before coma supervenes.

Eclampsia (7 cases, 0.6% of total cases of coma; mortality in this group, 42.8%). In 6 of these cases there had been convulsions before entry. In the seventh there had been severe intractable vomiting and toxic hepatitis was found at autopsy.

Miscellaneous (38 cases, 3.2% of total cases of coma; mortality in this group, 68.4%). There are many miscellaneous causes of coma. In our series these were: Erysipelas, 4; burns, 4; encephalitis, 3; brain tumor, 3; miliary tuberculosis, 2; carcinomatosis, 2; and 1 each of hypoglycemic shock (insulin), Stokes-Adams' disease, immersion, syncope, Simmonds' disease, Friedreich's ataxia, rupture of membranous urethra, pernicious anemia, hysteria, ruptured ectopic pregnancy, leukemia, cholemia, strangulated hernia, septicemia and empyema. In 5 cases a diagnosis could not be made. In many of these the coma was doubtless terminal. The rarity of cholemia, Stokes-Adams' disease, syncope and hysteria as causes of admission coma is noteworthy.

The 3 cases listed as encephalitis include 1 in which the symptoms followed shortly after an injection of vaccine, type unknown. In this case paralysis of all extremities and high fever soon led to coma and death. The second encephalitis case had its onset 7 years before, following measles. The patient had frequent attacks of coma following this, and was admitted in one such attack. The third was a boy, aged 14, who had had an upper respiratory infec-

tion for 2 weeks and entered after several convulsions. He remained mentally cloudy for 2 weeks, had high fever, diplopia and unequal pupils, but finally recovered. The patient with Simmonds' disease lapsed into coma in which he remained for 3 days, and then recovered. The patient with Friedreich's ataxia had an unexplained coma from which she also recovered. The patient with the ruptured membranous urethra had apparently incurred his injury 10 days previously when sounds were passed to dilate his urethral stricture. He entered with massive urinary extravasation and gangrene of the periurethral tissue and abdominal wall.

Summary. The records of 37,438 patients who entered the Boston City Hospital in 1933 were examined, and it was found that 1167 patients entered in coma. These cases were analyzed and the diagnoses eventually arrived at are tabulated and discussed. Of these 1167 cases, alcohol was responsible in 59.1%; trauma, in 13%; and cerebral vascular lesions in 10.1%. The last two made up more than one-half of the non-alcoholic comas. Other causes, each forming 3% or less of the total, in order of numerical importance were: poisoning, epilepsy, diabetes, meningitis, pneumonia, cardiac decompensation, exsanguination, syphilis of the central nervous system, uremia and eclampsia.

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SPONTANEOUS HEMOPHILIA.

REPORT OF SIX CASES IN BROTHERS.

By ROBERT BOGGS, M.D.,

RESEARCH FELLOW IN SURGERY, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

(From the Pathological Institute, McGill University, Montreal, Prof. Horst Oertel, Director.)

HEMOPHILIA is now generally regarded as an hereditary constitution, sex-linked and recessive. The factor for its inheritance is thought to be carried on one of the sex chromosomes, there being 2 such chromosomes in the human female and 1 in the male. In the male, in place of 1 X chromosome we are thought to have an altered chromosome, usually called Y. If hemophilia is a recessive character, the descent of the factor can be represented thus:

	Female.		Male.
Parent	X	X	X Y
Offspring	X X	X X	X Y X Y

From this it is seen that the affected X chromosome passes to 50% of male and female offspring; but in the female its effect is apparently offset by the presence of a normal X chromosome, and she thus escapes the symptoms of the disease. The daughters of hemophilic males are carriers, but the sons are not affected. From this it follows that the immediate inheritance of all hemophilic males must be from the mother. Theoretically, as a result of crossing a female carrier with a bleeder, one-half of the male offspring should be bleeders. The females of such parents should be half carriers and half hemophilic females. As no authentic case of hemophilia in a woman has been described, it has been suggested that such a combination may be incompatible with life. This is not the case, however, in the analogous hereditary condition of color blindness.

Hemophilia occasionally does appear with no known ancestral bleeders. It is then referred to as sporadic or spontaneous hemophilia. The origin of these cases has been the subject of much speculation. Actually, the explanation of these spontaneous hemophilias resolves itself to 3 definite possibilities: (1) That these cases arise *de novo*, and that the laws of transmission remain the same as in the usual type of this disease. This conception assumes sudden hereditary change which breeds true (often mis-called mutation).^{*11} (2) Long inheritance through the females with the males not showing hemophilia to the extent expected by the law of averages. This implies inherited constitutions coming from remote individuals far beyond the reach of the investigator, and that by chance alone the recognized males of such families have failed to receive the hereditary materials which cause the increased susceptibility to bleeding. This is in agreement with Bullock and Fildes⁴ (1911), who pointed out that skipping of generations probably does not occur, and designated such males as did occur in these families "as unaffected males." They further stated that they did not believe that the disease could arise *de novo*. (3) There is the error in the study of the genealogic tree, due to illegitimacy. The difficulties of investigation along this line are obviously almost insurmountable. It may be done by study of the blood groups. However, even in the rare instances where both maternal grandparents are available, in only about 50% of the cases would it be possible to demonstrate an existing error in the paternity of the mother.

The earliest report of cases of what was apparently genuine spontaneous hemophilia (blood studies were not introduced until 1901) was by Stoeck¹³ (1850), in which he reported 3 cases of bleeding with no other bleeder males in 3 previous generations.

For similar cases see Table 1, in addition to which there were

* Professor Oertel, in his *Outlines of Pathology*, points out that the original meaning of the word was gradual and directional, rather than sudden change.

many others who reported cases that, due to inaccuracies or insufficient data, could not be definitely established as genuine hemophilia.

TABLE 1.—REPORTED CASES OF SPONTANEOUS HEMOPHILIA.

Author.	Date.	No. of bleeders.	No. of generations without bleeders.	Remarks.
Stoehr ¹³	1850	3	3	
Grandidier ⁷	1855	5	3	
Barlow ³	1876	2	2	
Hansen, ^{8 a}	1886	4	2	
Hansen, ^{8 b}	1886	5	2	
Ripke ¹²	1889	1	3	
Kinnicutt ⁹	1905	1	4	
Albers ¹	1906	1	3	
Weil ¹⁶	1908	1	3	
Thompson ¹⁴	1911	5	4	
Gettings ⁶	1911	5	3	Extensive study of all collaterals.
Arrigoni ¹	1932	1	3	
Laclette ¹⁰	1932	1	?	
Fonio ⁵	1933	2	2	

It is in the examples where several children of a family apparently spontaneously develop the disease that particular interest lies, for in them it seems quite certain that the disease does not arise *de novo*, but that they must have inherited the disease from the recessive mother. Such an example is the subject of this report:

Family Record. In the family observed by the author for the past 3 years, there were 7 boys and 1 girl. The girl and 1 of the boys were normal; the other 6 boys suffered repeated hemorrhages following slight trauma. The bleeding on most occasions continued until they became practically exsanguinated and then stopped spontaneously. All have had hemarthroses of the knee joints following slight trauma. They appeared as normal children in periods between attacks. In all, the tendency to bleed appeared shortly after birth and has gradually lessened as they became older. Two of the boys affected died in infancy, 1 was killed in an accident and the other died of rheumatic heart disease. Blood studies were done on the youngest and oldest. The other children were not available.

The oldest son, aged 22, when seen 3 years ago, was bleeding from the urethra following violent exertion. The bleeding finally stopped spontaneously. He was again seen, in 1932, and came to the hospital* with a large cut on one of his fingers which seeped constantly. With a tourniquet in place, the wound was closed and a thick layer of collodion applied. These measures sufficed to stop the hemorrhage. During this visit a blood study was done. His coagulation time was increased ($\frac{1}{2}$ to 1 hour), the clot retracting normally. The bleeding time was normal (Duke); platelets were normal (200,000+ per c.mm.)

The youngest brother, aged 4 years, was in the hospital,† in 1931, at which time, a large abscess was opened over the right inferior margin of the mandible. Transfusions were necessary both before and after the operation. Blood studies then, and on many subsequent occasions, showed his coagulation time to be markedly prolonged (1 to 24 hours), the clot retracting. The bleeding time (Duke) was normal. The platelets

* Outdoor Department, St. Luke's Hospital, Montreal.

† Homœopathic Hospital, Montreal, Service of Dr. J. T. Novinger.

were consistently above 250,000. Despite the fact that the other brothers could not be examined, it is highly improbable that they suffered from any form of hemorrhagic diathesis such as essential thrombocytopenia, for that disease is not clearly familial.

The family history was taken from several members on separate occasions and their stories checked perfectly so that it is fairly dependable. The father's family history is irrelevant. The mother's family was known in its entirety through the 4th generation and, in addition, 2 members of the 5th. It was possible to get the names and a short history of each member of the family (see chart), since the family had resided in the same rural community for 5 generations. There was not the least tendency to bleed in any of the individuals shown in white on the chart. Most of them lived to advanced old age. There were potential bleeders (unaffected

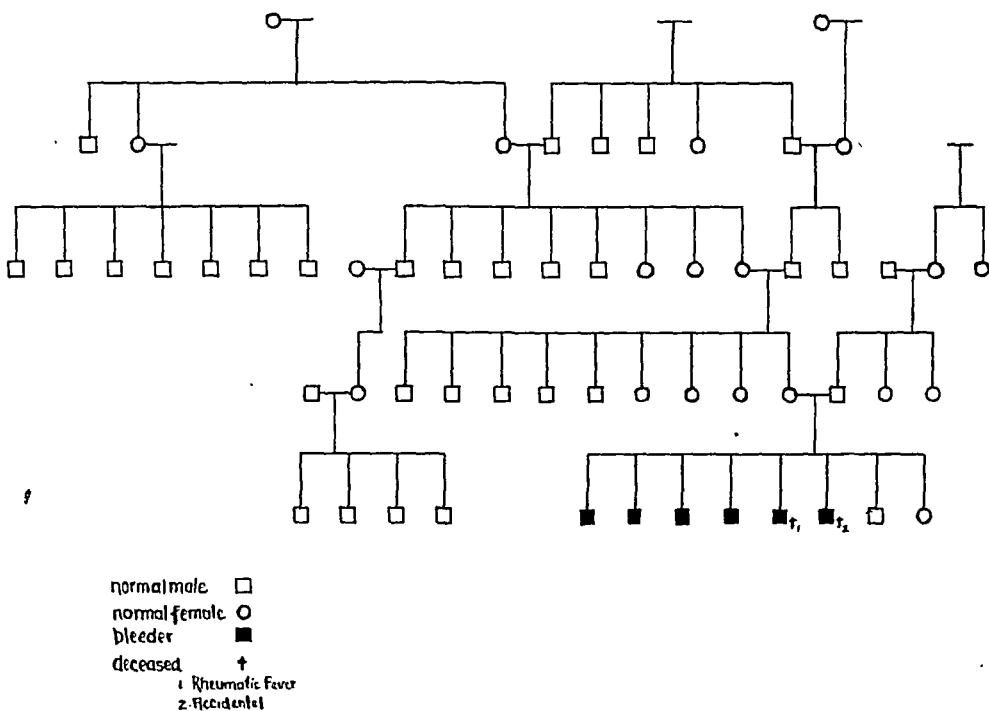


CHART I.—Family tree of hemophilic brothers.

males) in each stem of the family, if their respective mothers were carriers. The only female who was in the direct line of descent and did not have at least 5 sons was the great-great-grandmother of the patients, who had only 1 son. If we assume that the disease in this case did follow the Mendelian line of descent, then this woman must either have been a carrier or her husband was a bleeder. The history of the latter was not available. An incidental finding was that the grandparents of the patients were first cousins, but this could not alter the hereditary process in this disease.

It is barely possible that if this family and the other cases which have been reported could be traced to antiquity, an antecedent bleeder might be found. The occurrence, however, of such a large number of unaffected males would be truly remarkable, since theoretically 50% of the males in the direct female line should have

received the hereditary characters which make up the hemophilic constitution. In fact, the number is here so great that one would hesitate to attribute it to an extraordinary run of negatives under the laws of chance. We are inclined, therefore, to dismiss the possibility of hemophilia being concealed in this family for several generations and look for an explanation in one of the other two possibilities, namely, true spontaneous origin or illegitimacy. Between these it is impossible to draw positive conclusions. There seems to be no doubt that, with so many members of the family afflicted, we must look to the mother for our explanation. Either she is an example of the disease arising spontaneously in the female or she is illegitimate. Unfortunately, both of her parents are dead, so the possibility of investigating this point by the inheritance of the blood groups could not be undertaken.

Conclusions. An example of apparent spontaneous hemophilia in 6 brothers is reported. The large family tree on the mother's side practically precludes the possibility of concealed inheritance.

The author wishes to express his obligations to Prof. T. R. Waugh, in charge of the Department of Hematology in the McGill Pathological Institute, for the opportunity to study these cases, and for his many valuable suggestions.

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A FAMILIAL HEMORRHAGIC CONDITION SIMULATING HEMOPHILIA AND PURPURA HEMORRHAGICA.

BY JASON E. FARBER, M.D.,

SENIOR RESIDENT, BUFFALO CITY HOSPITAL, BUFFALO, N. Y.

(From the Buffalo City Hospital and the School of Medicine, University of Buffalo.)

RECENT literature has described certain hemorrhagic diatheses which cannot be classified with recognized types of such disorders. Glanzmann¹ described one such entity under the name "hereditary

hemorrhagic thrombasthenia." Eight families were afflicted with severe epistaxis and ecchymoses. Both sexes were involved and transmission was usually by the females. Blood studies were normal except for an occasional slightly prolonged bleeding time with an associated delay in clot retraction. Minot² reported 5 cases of this kind associated with an intermittent prolongation of the bleeding time. The symptoms were multiple ecchymoses and recurrent epistaxis. Cases somewhat similar have been reported by Buckman,³ Rothman and Nixon,⁴ and others.^{5,6,7,8} Little has been learned about the pathogenesis.

This communication presents an heretofore unrecorded family of similar "bleeders." These conditions are to be differentiated from hemophilia and purpura hemorrhagica (thrombopenic purpura, Table 1).

TABLE 1.—DIFFERENTIAL DIAGNOSIS OF HEREDITARY HEMORRHAGIC CONDITIONS.

	Sex involved.	Transmission through.	Site of bleeding.	Coagulation time.	Bleeding time.	Tourniquet test.	Clot retraction.	Platelet count.	Platelet resistance.
Hemophilia	Male	Female	Joints, skin and mucous membranes	Prolonged	Normal	Negative	Normal	Normal or increased	Increased
Thrombopenic purpura (purpura hemorrhagica)	Male and female	Male and female	Skin and mucous membranes	Normal	Prolonged	Positive	Delayed	Diminished markedly	Normal
Thrombasthenic purpura	Male and female	Female usually	Skin and mucous membranes	Normal	Prolonged	Positive	Delayed	Normal	Decreased
Hereditary telangiectasia	Male and female	Male and female	Mucous membranes and skin	Normal	Normal	Negative	Normal	Normal	Normal
Reported condition	Male and female	Male and female	Skin and mucous membranes	Normal	Intermittently prolonged	Negative	Occasionally slightly delayed	Normal	Normal

Results of Present Study. This condition has affected at least 14 males and 11 females during 5 generations, comprising more than 100 members. The genealogic tree of the family (Chart I) shows the occurrence of the bleeding tendency in the successive generations. The males have been more markedly affected, and have often been considered hemophiliacs. Their bleeding experiences have been varied, including those following operations such as tonsillectomies, tooth extractions and circumcision, and those associated with slight trauma. Other manifestations have included epistaxis and numerous ecchymoses or purpuric spots, both spontaneous and traumatic, in some instances covering large areas of the body. The females have characteristically suffered with menorrhagia, multiple traumatic ecchymoses and in some cases epistaxis.

The disturbance is usually observed at about puberty in the females and somewhat earlier in the males. It is generally more

severe when the individual is younger and seems to lessen in severity as age increases. The affliction, however, varies in degree of severity, some members being involved much less than others. Many

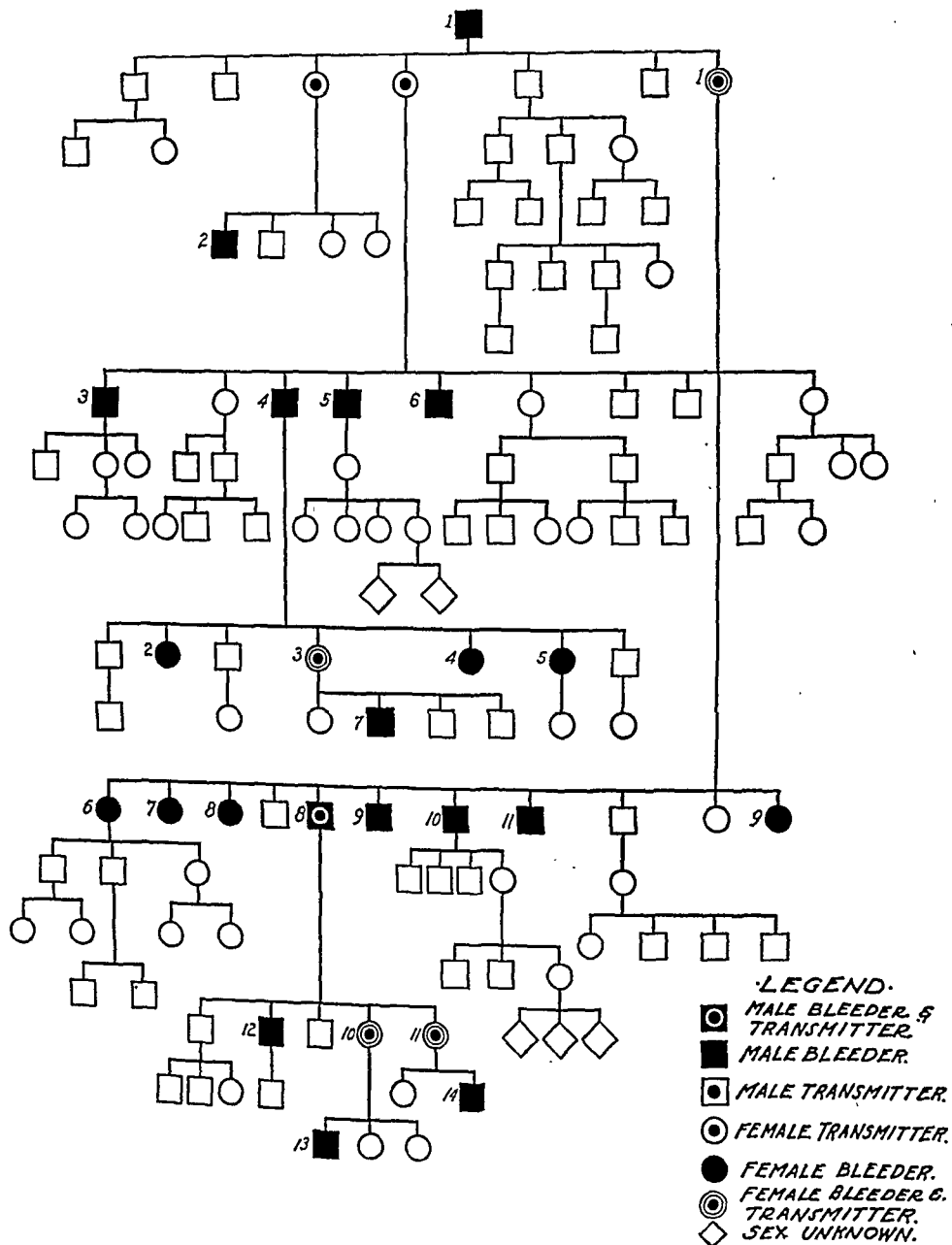


CHART 1.—Genealogic tree of reported family.

of the males have suffered hemorrhages until almost exsanguinated, while at other times the bleeding has been moderate. Death due directly to the bleeding can be ascribed in only 4 cases. "High

blood pressure" is known to "run in the family" and cerebral vascular accidents have been a common cause of death in several of the "bleeders."

Both males and females are transmitters. The female apparently transmits the more severe form of this disorder, directly to her sons from her father. This form of transmission is compatible with the genetics of hemophilia but in hemophilia the female is not involved. However, in the condition described here, the mothers of male "bleeders" exhibit the purpura to a great extent. Furthermore, males never transmit hemophilia, and in more than three score of severe bleeding experiences, no male ever developed a hemarthrosis.

As regards laboratory examination, no affected individual in our study has had a prolonged clotting time (method of Lee and White). The bleeding time (method of Duke) has occasionally been slightly prolonged, between bleeding phases. At this time the platelets are somewhat lower than normal and clot retraction is slightly delayed. Following a bleeding phase the blood picture shows an anemia and a normal leukocyte count. Sedimentation rate and blood chemistry are normal. The tourniquet and flicking tests are negative. (Controls in all the above tests included normal individuals and 1 known true hemophiliac.)

Case Abstracts. The following is a more detailed description of the affected individuals.

M (male bleeder) 1, lived in Alsace-Lorraine. He suffered from uncontrollable bleedings from any site of injury on the body, had epistaxis, numerous ecchymoses and a fatal traumatic epistaxis. *M 2*, *M 5*, *M 10*, and *M 11* had numerous severe bleeding episodes, throughout life, from all parts of the body, usually following trauma and tooth extraction. Epistaxis and ecchymoses were common. *M 10* and *M 11* are said to have died from brain hemorrhage when about 50 years of age. *M 3* was admitted to the Buffalo City Hospital on November 6, 1923, bleeding from the gums. This condition had continued unabatedly for 15 days following extraction of 8 teeth and the patient was *in extremis*. Physical examination was otherwise negative except for the marked anemia. The spleen was not palpable. The blood showed a hemoglobin of 45%, red cell count 2,500,000 per c.mm.; the clotting time was 7 minutes. Blood urea was normal; urine, Wassermann test and gastric analysis were negative; the stool showed a 3+ occult blood. History revealed that the patient had throughout his life suffered hemorrhages, ecchymoses and epistaxis following even trivial trauma. The patient recovered from this experience but died 5 years later from "apoplexy."

M 4 was seldom free of ecchymoses. He had prolonged bleeding following "cuts," and epistaxis, on one occasion lasting 18 hours. Death occurred suddenly from a "stroke."

M 6, at the age of 22 months, bit his tongue and bled to death in spite of surgical intervention. *M 7*, aged 17, was admitted to the Buffalo City Hospital on September 21, 1932, with a large subperiosteal hematoma of the left leg, traumatic in origin. In the past the patient had bled profusely following circumcision at the age of 5 (a transfusion was required to check the hemorrhage); following tonsillectomy, tooth extractions and trauma, and has also had numerous ecchymoses. Physical examination showed a well developed and nourished youth with no abnormalities except for the

hematoma. The spleen was not palpable. The blood count showed a slight secondary anemia with a normal white cell and differential count. The bleeding time was 8 minutes; clotting time 8 minutes. The urine, Wassermann test and Roentgen ray plates of the left leg and ankle were negative. Temperature, pulse and respirations during 25 days' stay in the hospital were normal. On two occasions during the past year the patient had prolonged bleeding from cut fingers and recently developed an extensive ecchymosis of the eyelids and forehead following a slight injury. Repeated bleeding and clotting times, however, were normal. The platelet count on one occasion was 164,000 and clot retractility at this time was perhaps slightly delayed. A blood count on January 4, 1934, showed a normal hemoglobin, red and white cell count with a relative lymphocytosis. The patient's diet has apparently always been well balanced and includes an ample supply of meat, milk, fruits and vegetables. Skin tests with powdered group extracts of meat, fowl and fish were negative.

M 8, aged 47, an office clerk, was admitted to the Buffalo Deaconess Hospital in 1921, in a state of collapse, with a diagnosis of internal hemorrhage and died 18 hours later. Roentgen ray revealed dense fluid shadow in left pleural cavity. At *autopsy* the patient's abdomen was said to have been found filled with fresh blood, but no autopsy record is now available. The patient was considered a "bad hemophilic." His life had been marked by many hemorrhages, both spontaneous and traumatic. Shaving was invariably followed by actual "streams of blood." "Black and blue spots" were constantly present and, on several occasions, extensive suffusions occurred, covering large areas of the body. Oozing of blood from various parts of the body frequently occurred. On one occasion the patient began oozing from the feet. This continued for several days. The patient's diet was apparently well balanced and bleeding episodes occurred throughout the year. Unfortunately, no laboratory studies are available.

M 9, aged 21, died from a traumatic epistaxis. His bleeding episodes corresponded to those of his brothers, *M 10* and *M 11*.

M 12, aged 33, the son of *M 8*, since the age of 5 has had numerous periods of prolonged bleeding from cut fingers, epistaxis, and from tooth extractions. Shaving has always been attended by bleeding and oozing in appreciable amounts. The patient's diet has apparently been well balanced and bleedings occur throughout the year. The bleeding condition, however, has of late become less severe which, the patient notes, is "ever since I stopped having boils." Physical examination on November 27, 1933, revealed a large, well built man, and no abnormal findings were demonstrable. Blood count showed a normal hemoglobin, red and white cell counts with a relative lymphocytosis. Platelet count was 350,000; the clotting time 7 minutes (control 7 minutes); bleeding time 4 minutes; clot retractility normal; prothrombin time (method of Howell) 12 minutes; the Wassermann and Kahn tests were negative. The blood calcium and phosphorus were normal in amount; the sedimentation rate was normal and the tourniquet test was negative.

M 13, aged 6, grandson of *M 8*, was admitted to the Buffalo City Hospital (service of Dr. F. J. Gustina) on November 4, 1933. The patient had been bleeding and oozing from the gums for 10 days following tooth extraction, and on the day of admission had suffered a traumatic hematoma of the forehead. Past history revealed a series of hemorrhages and ecchymoses which began at the age of 2. The patient's diet has always been well balanced. Bleeding episodes have occurred at all seasons of the year. The patient generally was in a healthy state at the time of bleeding. Physical examination showed a well developed and nourished, rather pale appearing boy of 6. He displayed a soft subcutaneous hematoma the size of a horse chestnut in the middle of the forehead, and oozing from the

gums. No telangiectasia could be found. The spleen was not palpable. After a short stay in the hospital the patient was much improved. Laboratory studies were as follows: Blood count on November 6, 1933: Hemoglobin, 68% Sahli; red cell count, 3,420,000; white cell count, 7750; the differential count showed a slight shift to the left; blood platelets, 160,000; the bleeding time, 6 minutes; clotting time, 3 minutes (capillary pipet method); the sedimentation rate, normal. Blood count on November 16, 1933: Hemoglobin, 70% Sahli; red cell count, 4,270,000; white cell count, 6900; the differential count showed a moderate increase in lymphocytes; platelet count, 230,000; clotting time, 7 minutes; prothrombin time, 12 minutes (control, 12 minutes); bleeding time, 3 minutes; clot retraction complete in 24 hours. The blood calcium, phosphorus, sugar, urea, cholesterol, chlorids and carbon dioxid combining power were normal; the tourniquet and flicking tests were negative; the urine and Wassermann tests were negative. A high-protein diet was instituted and greater care taken to avoid trauma. Subsequent studies have shown a consistently normal bleeding and clotting time, platelet count and clot retractility. During this time the ecchymoses have become fewer.

M 14, aged 6, grandson of *M 8*, has had many bleeding experiences since infancy; one of these, following circumcision, required transfusion.

F (female bleeder) 1, F 2, F 3, F 4, F 6, F 7, F 8 and F 9 throughout their lives suffered from menorrhagia and ecchymoses. *F 3* has a menstrual fraction of 14(5-7)/26. Physical examination on February 20, 1934, revealed no abnormalities. Bleeding time, clotting time and clot retractility were normal; the tourniquet and Wassermann tests were negative.

F 5 had ecchymoses, menorrhagia and frequent epistaxis.

F 10, aged 31, mother of *M 13*, has bruised easily as far back as she can remember. Since puberty she has suffered from menorrhagia. Her menstrual fraction is 11(7-10)/21-28. Physical examination was essentially negative, the spleen was not palpable and no telangiectasia was demonstrable in the nose, on the gums or on the skin. Laboratory studies include: the blood on March 8, 1934, showed a normal hemoglobin, red, white and differential count; platelets, 150,000 (method of Wright); bleeding time, 4 minutes; clot retraction normal; clotting time, 7 minutes (Lee and White); the tourniquet and flicking tests negative; platelet count (March 29) was 202,000.

F 11, aged 29, mother of *M 14*, suffers epistaxis, menorrhagia and ecchymoses. These appear more severe since she has lived in the South (Florida).

Discussion of Findings in Present Series. Here, then, is a family, Germanic in origin, tainted with a hemorrhagic state. Of the 131 individuals, 71 are males, 55 are females and the sex is unknown in the remaining 5. Fourteen (20%) of the 71 males have lived or are living a life frequently interrupted by bleeding episodes; these were directly the cause of death in 4 cases. The source of the bleeding has been diverse, the skin and mucous membranes being chiefly involved. Eleven (20%) of the 55 females have manifested the hemorrhagic taint chiefly by excessive bleeding from the uterus and under the skin. This has been of serious import in only 1 case, whereas in the remainder it has been merely temporarily disabling. On the whole the females are far less severely afflicted than the males, although the occurrence of the disease is roughly the same in both sexes. No telangiectasia has been found and splenomegaly is absent. There is no definite seasonal incidence

of the bleeding episodes. All the male members of the family have been occupied by work of either a clerical or farming nature; the females have been principally housewives. There has been no undue exposure to unhygienic conditions. Trauma has been the principal factor in precipitating the hemorrhagic event, while infection has been associated in only a few cases. The diet has apparently been ample and well balanced in meats, fruits, vegetables and carbohydrates. There are no food idiosyncrasies in the family. Laboratory studies have only served to rule out the common and recognized forms of hemorrhagic states as the diagnosis in this case. Clinically there is prolonged bleeding and this brings the patient to the physician. Unfortunately examination of the patient is usually at a lesser or greater period of time after the bleeding event.

The frequent occurrence of hypertension and brain hemorrhage in the successive generations is worthy of note. At least 15 unaffected members of the family have been patients at the Buffalo City Hospital for various ailments. None of these exhibits to any degree the tendency to the pathologic hemorrhage of their relations.

Twelve of the affected males are grandsons of "bleeders," the transmission being by the female. Four of the 6 mothers of these 12 "bleeders" suffer from the purpuric condition; data on the remaining 2 are unavailable. In only one instance an affected male (*M 12*) is the son of a male "bleeder." Six of the affected females are sisters of male "bleeders" and Pratt⁹ notes that sisters of hemophiliacs often suffer with purpura. The genealogic tree in regard to the males, with the exception of *M 12*, resembles that of hemophilia. Wyllie and Ellis¹⁰ state that isolated features of purpura occur in certain hemophiliacs and *vice versa*. However, the familial affliction is chiefly purpuric in nature, and because of the similarities to the two apparently distinct hemorrhagic disorders, *i. e.*, hemophilia and purpura hemorrhagica, no diagnosis can be made with certainty in these cases. Perhaps this is in keeping with the idea advanced by Aschoff and others¹¹ that the name applied to the hemorrhagic diathesis is of secondary importance, for the underlying defect, which is all-important, probably lies in the reticulo-endothelial system. Furthermore, evidence suggests that this defect may, in instances, be genotypic, *i. e.*, carried in the germplasm.

Conclusions and Summary. This study presents a family of more than 100 members during 5 generations, of which 25 members suffer atypical pathologic hemorrhage. Fourteen (56%) of the 25 are males; 11 (44%) are females.

The family tree in regard to the males has striking similarity to that of hemophilia, but the affliction is essentially purpuric in nature. The males have been more markedly involved, 4 of their number dying directly from hemorrhage.

The hemorrhagic incidents are variable, but consist chiefly of

prolonged frank bleeding from a cut or wound, ecchymoses and epistaxis in the males and menorrhagia and ecchymoses in the females. The coagulation time of the blood is normal; bleeding time is intermittently prolonged; platelets are numerically adequate and the clot retracts normally. Blood chemistry is normal.

There seems to be no definite relation of the bleeding to season, diet, infection or occupation.

Telangiectasia and splenomegaly are uniformly absent.

Hypertension "runs in the family;" brain hemorrhages are frequent.

No diagnosis is attempted; further studies are in progress.

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ELONGATION OF THE RED BLOOD CELLS IN A JEWISH FAMILY.

By LEO H. POLLOCK, M.D.,

INTERN, SURGICAL SERVICE, BETH ISRAEL HOSPITAL,

AND

WILLIAM DAMESHEK, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, TUFTS COLLEGE MEDICAL SCHOOL; ASSOCIATE PHYSICIAN, BETH ISRAEL HOSPITAL,
BOSTON, MASS.

(From the Surgical and Medical Services and the Department of Pathology, Beth Israel Hospital.)

THE human red blood cells are so consistently round that any constant deviation from their normal shape excites interest. Irregular variation in shape occurs in several types of anemia, but this is apparently of different significance from the consistently abnormal appearance of the red blood cells seen in sickle-cell anemia and in the associated states of "sicklemia" without anemia and "ovalocytosis." The occurrence of sickle-shaped erythrocytes in the blood

has for so long been associated with the negro race that the possibility of its appearance in the white race is still not generally known. The finding, therefore, of large numbers of oval, elongated and even sickled red blood cells in several members of a Jewish family in whom there was apparently no admixture of negro blood seemed of sufficient interest to warrant this report.

Various observations were made regarding the mechanism of the ovalocytosis, during the course of which the experiments of several investigators were repeated. A critical review of the literature bearing on the occurrence of elongated red blood cells, particularly in the white race, was made.

Case Abstract. Esther L., a single, white Jewess, aged 30, entered this hospital for the removal of a painless lump in the breast. She was born in Chelsea, Mass., and had always lived there or in the nearby city of Somerville. She had never been ill. On examination, she was found to be in excellent physical condition. In the upper outer quadrant of the left breast was a hard, painless, non-tender, nodular mass with an accompanying enlarged lymph node in the left axilla. Roentgen ray of the long bones and the chest failed to reveal any metastases. A radical resection of the left breast was performed. Pathologic report showed chronic cystic mastitis with carcinoma simplex and axillary metastases. Thirteen days after operation, a Thiersch graft was made following which the patient had an uneventful convalescence.

During the course of a red blood cell count a large number of elliptic and oat-shaped red blood cells was noted. Certain investigations were thereupon carried out, which are described below.

Results of Investigations. 1. **FAMILY.** The patient was one of 4 children born of Russian-Jewish parents (Western Russia), who had emigrated to Massachusetts in 1890. Due to lack of coöperation, detailed information concerning the family tree was not obtained. It seemed highly improbable, however, that any admixture of negro blood had occurred in this typical Jewish family. The father died in an accident about 20 years previously; no information regarding his consanguinity could be obtained. The mother, Anna, aged 62, had gray hair, blue eyes and a light complexion. She had been known to have mild diabetes mellitus for several years. A sister, Beatrice, aged 28, was tall and thin, had blue eyes and light-brown hair. She complained of being "highstrung" and had suffered from anorexia and fatigue for many years. She did not allow physical examination but appeared rather sallow and very nervous. A brother, Irving, aged 38, had always been well and seemed so on inspection; he also refused examination. Another brother lived in Joliet, Ill. Attempts to communicate with him were unsuccessful. The patient, Esther, had blue eyes, light-brown hair which was perfectly straight, a straight nose and thin lips. None of the members of the family possessed any negroid characteristics.

2. **ROUTINE LABORATORY STUDIES** (Table 1). Except for the abnormality of the red blood cells described below, routine labora-

tory studies failed to reveal anything of note. It is interesting that all of the members of the family studied belonged to Group II (Moss). The mother showed slight elevation of the blood sugar level.

TABLE 1.—BLOOD STUDIES IN 4 MEMBERS OF A FAMILY.

	Esther (patient).	Anna (mother).	Beatrice (sister).	Irving (brother).
Hemoglobin	90	90	87	92
Red blood cells, millions	5.2	4.65	4.32	4.75
White blood cells	14,400	6400	10,800	6900
Platelets	812,000			
Reticulocytes, %	2.3			
Blood group (Moss)	II	II	II	II
Fragility of red cells	0.44-0.34	0.46-0.36
Sedimentation rate, mm. per min.	1.05			
Mean corpuscular volume	78			
Blood sugar	75	185	..	74
Non-protein nitrogen	30			
Icterus index	5			7.5
Quantitative bilirubin, mg. per 100 cc.	0.3	0.5

3. STUDIES OF THE RED BLOOD CELLS. A. *Morphology.* The red blood cells varied markedly in their morphologic appearance. This was particularly true in the cases of Esther and Beatrice. The mother's red blood cells showed but little deviation from the normal round shape; the brother's cells showed moderate elongation.

The red blood cells could be arbitrarily divided into the following groups: round, oval, elongated and sickled. The round cells had the same diameter throughout. The oval cells presented one diameter definitely longer than the other; in measurement they varied from 6 by 8 micra to 4 by 9.5 micra. The elongated cells usually appeared as cigar-shaped forms, measuring 2 by 10 micra in size. The so-called "oat cells" of certain authors were included in this category. These presented long pointed ends from which extended a long filament. The sickle-shaped cells were characterized by their definitely curved banana or sickle-shaped appearance. The amount of curvature of the cell varied from an arc of 10 degrees to one of 170 degrees.

TABLE 2.—TYPES OF RED BLOOD CELLS IN THE SUBJECTS STUDIED.

	Round, %	Oval, %	Elongated, %	Sickled, %
Esther:				
0 hr.	41	32	20	7
24 hrs.	15	45	39	1
Beatrice:				
0 hr.	8	62	26	4
24 hrs.	5	64	30	1
Irving:				
0 hr.	35	53	9	0
24 hrs.	20	71	9	0
Anna:				
0 hr.	98	1.5	0.5	0
24 hrs.	96	2.0	2.0	0

The abnormalities in shape of the red blood cells could be best observed in fresh, unfixed preparations of blood spread under a thin coverslip rimmed with vaselin, and in supravital preparations stained with Dameshek's platelet-reticulocyte solution.¹

B. Quantitative Aspects. 1. *The Effect of Time Upon the Sickling Phenomenon.* The percentage of abnormally shaped red blood cells when blood was first drawn varied in each subject from day to day. In the case of Esther, the cells in which one diameter was longer than the other varied from 3% to 62%; in Beatrice, they were higher, from 80% to 92%; in Irving, from 48% to 62%; and in Anna, the mother, from 0% to 2%. Since the mother at no time showed any sickle-shaped cells, it is probable that her red blood cells were within normal morphologic limits.

Despite the variation in the number of abnormally shaped red blood cells from day to day in the freshly drawn preparations, it was striking to note that the end results of allowing the preparations to remain at room temperature for 24 to 28 hours were always approximately the same (Table 3). The greatest incidence in abnormal forms occurred at 48 hours, although there was but little difference in the number of these forms at 24 and 48 hours. After 48 hours and usually after 72 hours, the cells began to assume a rounded appearance, and after a week at room temperature, only an occasional oval or elongated cell was seen (Table 4).

TABLE 3.—VARIATION IN PERCENTAGES OF DIFFERENT TYPES OF RED BLOOD CELLS IN SUBJECT, ESTHER, ON DIFFERENT DAYS.

	Round, %	Oval, %	Elongated, %	Sickled, %
May 3:				
0 hr.	52	28	14	6
24 hrs.	15	46	32	7
June 15:				
0 hr.	34	45	20	1
24 hrs.	15	45	39	1
June 26:				
0 hr.	39	30	25	6
24 hrs.	18	42	41	9

TABLE 4.—EFFECT OF TIME OF STANDING ON SHAPE OF RED BLOOD CELLS IN SUBJECT, ESTHER.

Hours.	Round, %	Oval, %	Elongated, %	Sickled, %
0	97	3	0	0
2	84	12	4	0
20	4	59	35	2
24	0	45	45	10
30	0	22	63	15
45	0	2	78	20
72	8	20	54	18
120	30	45	21	4
144	70	12	17	1

2. *The Effect of Temperature.* The temperature at which the preparation was kept affected somewhat the rate of anisocytosis, and possibly its degree. Thus, when a preparation of fresh blood was placed in a refrigerator, elongation of the red blood cells became definitely diminished and fewer red blood cells were abnormal at the end of 24 hours. At incubator temperature (37.5° C.) there appeared to be a slight increase in the rate of anisocytosis as compared to that at room temperature (24° C.) (Table 5).

TABLE 5.—EFFECT OF TEMPERATURE ON THE MORPHOLOGY OF THE RED BLOOD CELLS.

	5° C.			21° C.			37.5° C.		
	Round, %	Oval, %	Elongated, %	Round, %	Oval, %	Elongated, %	Round, %	Oval, %	Elongated, %
0 hr.	33	29	28	33	38	29	45	35	20
18 hrs.	31	38	31	18	40	42	4	46	50
24 hrs.	74	18	8	20	36	44	12	40	48

3. *The Effect of Mechanical Factors.* Abnormally shaped cells were found in various parts of all preparations. This was particularly noted because of the statements made by various authors (see Discussion) that sickling occurred most commonly in the center of a preparation, *i. e.*, farthest away from the source of oxygen supply. The effect of *pressure* upon the development of deformity of the red blood cells has been commented upon by various observers. The abnormally shaped red cells appeared to be definitely more plastic than the round cells. Pressure upon certain sections of the preparation which contained many round cells caused a definite increase in the rapidity of appearance of the elongated cells. However, the end result after 24 hours was the same whether or not compression had been used. Pressure upon oval and elongated cells frequently brought about the appearance of various bizarre forms, which retained their shape for 2 to 10 minutes. It seemed probable that pressure caused the development of elongation somewhat more rapidly in those cells which already possessed the latent tendency to become elongated.

4. *The Effect of Roentgen Rays.* This was observed by two methods: (1) Fresh preparations of blood were exposed (*a*) immediately for 2 hours and (*b*) after standing at room temperature to deeply penetrating Roentgen rays; and (2) preparations of blood were obtained at regular intervals from the patient while she was receiving deep Roentgen ray therapy of the axilla by the Coutard method. No definite effect on the rate or extent of elongation of the red blood cells was noted (Table 6).

5. *The Effect of Various Substances.* (*a*) *Anticoagulants.* Fresh wet preparations made from blood mixed with heparin, sodium oxalate and Hayem's solution developed about the same degree of deformity on standing at room temperature as did fresh preparations made without the use of an anticoagulant (Table 7).

(*b*) *Various Concentrations of Salt Solution.* "Fragility tests" were performed with various concentrations of sodium chlorid in two subjects, Esther and Irving. With Esther the red cells began to hemolyze at 0.42%, hemolysis becoming complete at 0.34%. With Irving, the figures were 0.44% to 0.36%. The number of oval and elongated cells in the most dilute salt solutions was

definitely diminished (Table 8), indicating that the abnormally shaped red cells were slightly more fragile. "Shadows" of the elongated red blood cells could be observed in the partially and completely hemolyzed preparations suggesting that these cells, as well as the more normal round ones, had a definite structure or stroma not dependent upon such transient factors as external pressure or anoxemia.

TABLE 6.—EFFECT OF EXPOSURE (a) OF RED BLOOD CELLS TO ROENTGEN RAYS, (b) OF THE PATIENT TO ROENTGEN RADIATION UPON THE CELLULAR MORPHOLOGY.

(a) Fresh Preparations Exposed to Roentgen Rays.						
Time of exposure.	0 hr.		4 hrs. after exposure.		24 hrs. after exposure.	
	Oval, %	Elongated, %	Oval, %	Elongated, %	Oval, %	Elongated, %
0	38	24	39	32	44	41
30 min.	29	36	34	40	38	44
60 min.	34	28	38	31	44	39
90 min.	38	18	41	24	36	46
120 min.	21	29	26	34	34	43

(b) Patient Given Roentgen Ray Therapy.						
Length of time of Roentgen ray therapy (Coutard method).	Fresh.		4 hrs.		24 hrs.	
	Oval, %	Elongated, %	Oval, %	Elongated, %	Oval, %	Elongated, %
6/12 0	54	16	58	22	58	29
6/15 1 hr.	45	20	47	24	51	32
6/16 1½ hrs.	30	15	36	22	30	20
6/26 6 hrs.	30	25	33	38	42	41
7/6 7½ hrs.	56	28	54	32	61	29

TABLE 7.—EFFECT OF ANTICOAGULANTS ON THE PERCENTAGES OF ABNORMALLY SHAPED RED BLOOD CELLS.

	Fresh.			Heparin.			Sodium oxalate.			Hayem's solution.		
	Oval, %	Elongated, %	Sickled, %	Oval, %	Elongated, %	Sickled, %	Oval, %	Elongated, %	Sickled, %	Oval, %	Elongated, %	Sickled, %
0 hr.	28	31	1	20	38	0	36	35	1	42	33	1
24 hrs.	44	44	4	36	48	1	40	47	3	49	32	1

TABLE 8.—EFFECT OF OSMOTIC TENSION ON OVAL CELLS.

% NaCl.	Esther.		Irving.	
	Oval, %	Elongated, %	Oval, %	Elongated, %
0.46	16	4	42	16
0.44	20	12	32	5
0.42	22	16	43	10
0.40	26	11	40	10
0.38	32	4	24	1
0.36	26	6	Hemolyzed	

(c) Various Chemicals. Traces of potassium cyanid in heparinized blood produced a rapid increase in the development of oval

cells, so that within 7 minutes 80% to 90% of the red blood cells were oval in shape. However, after 25 minutes, the red cells appeared to develop a thick membrane and to lose their pliability. Marked elongation of the red blood cells did not occur in these preparations.

A drop of a 10% aqueous solution of *picric acid* added to 2 cc. of heparinized blood caused some of the oval red blood cells to become rounded, although no effect on the elongated cells could be seen.

(d) *Effect of Certain Gases.* Hahn and Gillespie² concluded, after extensive investigation, that sickling of the red blood cells occurred with conditions of anoxemia. They devised a method for permitting the cells to come in contact with the gas to be tested. This method, in simplified form, was used in our investigations.

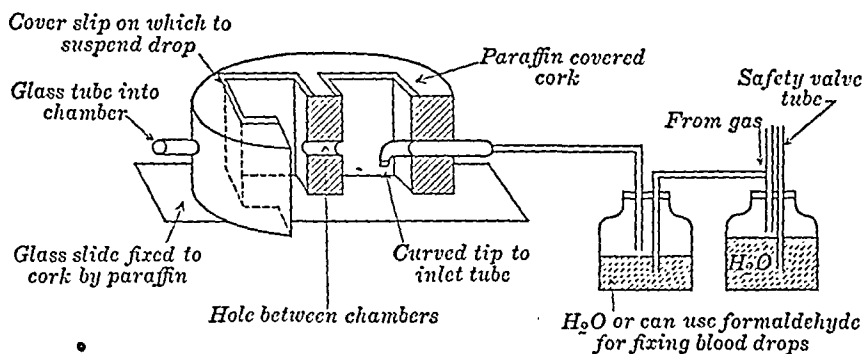


FIG. 1.—Schematic three-quarters cross section of gas compartments and of gauge bottles.

Method. Two "gas chambers" were constructed from a large cork (3 in. in diameter and 1 in. long) by punching 2 square holes just large enough to fit vaselin-rimmed coverslips over each. A small hole running through the diameter of the cork (Fig. 1) connected the 2 compartments. Into each compartment projected a small glass tube with a curved end. These tubes could be so adjusted by turning them that the incoming gas might play either directly on the hanging drop or into any portion of the chamber. The entire cork was thoroughly covered with a thin layer of melted paraffin and fastened by means of paraffin to a glass slide. Since the ends of the slide projected at either side of the cork, the entire apparatus could be placed on the microscope and moved about by means of the mechanical stage. Drops of blood treated with a suitable anticoagulant were placed on coverslips which were rimmed with vaselin and inverted over the 2 chambers. Examination was made with the high dry lens. The coverslips could be removed at any time for preservation. The various gases were passed into the chambers after preliminary passage through bottles partly filled with water. This procedure served not only to moisten the gases but to act as a pressure valve. Exit of the gases took place by means of an outlet tube. It was found in practice that oxalated blood prevented positive results and that if the heparinized blood was diluted slightly (25%) with Hayem's solution, rouleaux formation of the red blood cells could be prevented. Red cells from another subject could be used in 1 of the 2 compartments as a control during each experiment.



FIG. 2.—Stained blood smear of patient, Esther L. ($\times 800$.) Note the marked variation in shape of the red blood cells with the numerous oval forms and the occasional elongated (*E*) forms. One red blood cell (*S*) shows slight sickling.

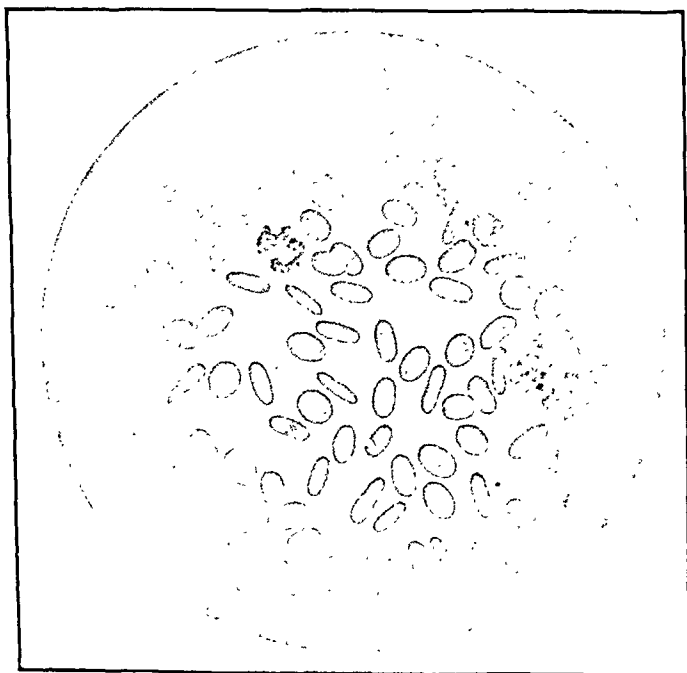


FIG. 3.—Stained blood smear of Beatrice L. ($\times 800$.) The tendency to elongation of the red blood cells is greater than in the case of Esther.

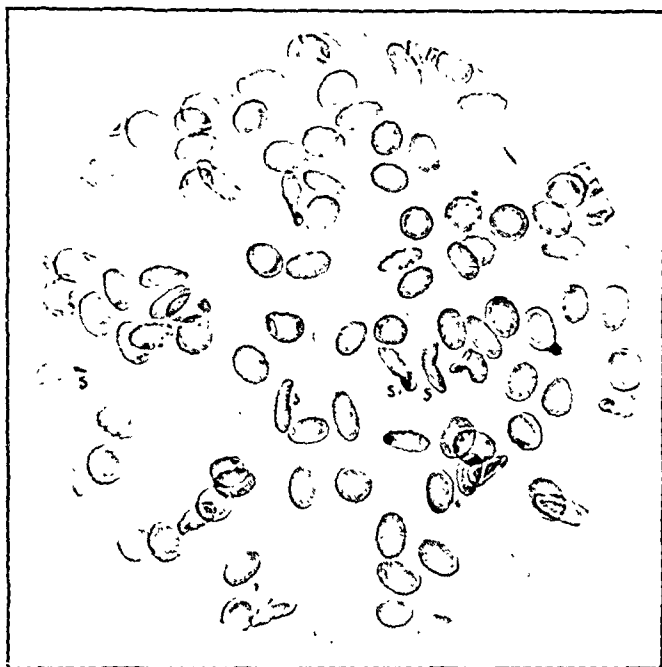


FIG. 4.—Fresh preparation of blood from patient, Esther L., after standing at room temperature for 3 hours. The cells marked *S* show a slight sickling tendency. ($\times 800$.)

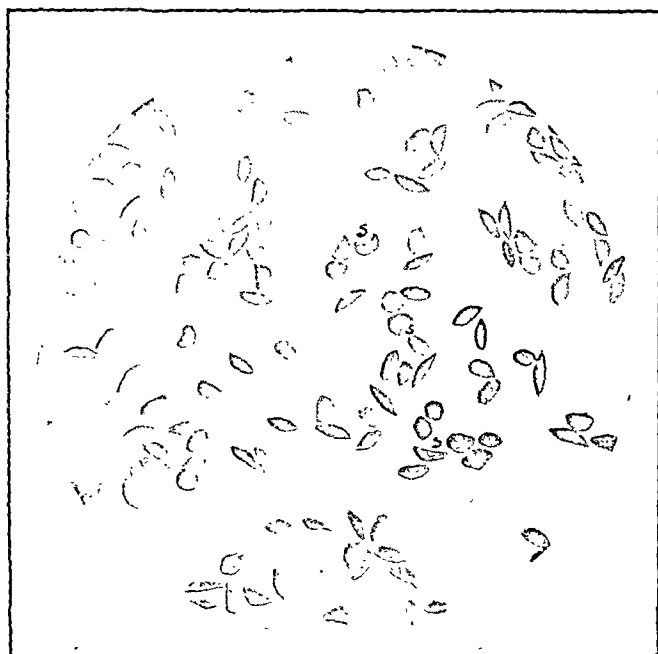


FIG. 5.—Moist preparation of blood from patient, Esther L., after standing at room temperature for 24 hours. ($\times 500$.) Note that the great majority of the red blood cells are normally shaped and that several have assumed a "sickle" shape (*S*). Filaments projecting from the ends of certain of the cells may be noted.

1. *The Effect of Carbon Dioxid.* Carbon dioxid passed into the gas chamber for 10 minutes caused striking elongation in the great majority of the red blood cells. After 25 minutes of exposure, the cells became rounded and appeared slightly swollen.

When oxygen was passed into the chamber at the time when most of the red cells had become elongated, no reversal to the initial round or oval forms was accomplished. This observation is contrary to the experience of Hahn and Gillespie.²

In certain experiments the elongated forms were fixed by passage of formaldehyde gas into the chamber. (This gas was produced by passing the carbon dioxid gas through a bottle containing a warm 40% solution of formalin.) The suspended drop was then carefully and slowly dried by playing the formaldehyde gas directly into it. Slow drying was found necessary for proper fixation.

2. *The Effect of Nitrous Oxid.* Nitrous oxid caused an increase in the percentage of oval forms, although no increase in the number of elongated cells took place.

3. *The Effect of Oxygen.* The failure of oxygen to alter the shape of the elongated cells produced by carbon dioxid has already been noted. No increase in anisocytosis took place when blood was drawn from a finger made cyanotic for 15 minutes by the application of a tourniquet; subsequent oxygenation of this blood in the above-described gas chamber caused no change in their appearance. Again, no alteration in shape occurred when blood flow was stimulated by immersing the hand in warm water before the finger was pricked.

The effect of increasing the oxygen content of the blood was studied by placing the patient in an oxygen tent in which the oxygen content of the air was approximately 45%. Three hours' constant stay in this tent produced no diminution in the number of oval or elongated forms.

TABLE 9.—RELATION OF ANEMIA TO ABNORMALLY SHAPED CELLS.

Date.	Hemoglobin (Sahli), %	R.B.C., millions.	Abnormally shaped red blood cells, %		
			Oval.	Elongated.	Sickled.
5/3	90	5.20	A 28	14	6
			B 46	32	7
5/17	60	2.75	A 47	38	7
			B 32	49	4
5/24	65	2.61	A 63	12	0
			B 61	24	0
6/12	52	2.90	A 45	20	1
			B 45	39	1
6/16	64	3.10	A 30	15	0
			B 39	20	1
6/26	80	4.25	A 30	25	6
			B 42	41	9
7/16	82	4.60	A 56	28	2
			B 61	32	1

(c) *Effect of Anemia.* Opportunity presented itself in the patient, Esther, to study the proportion of abnormally shaped red cells not only when the erythrocyte count was normal, but when

she developed a moderate degree of anemia following operation. The greatest proportion of oval and elongated cells in freshly drawn blood was present when the red blood cell count was at its lowest level (2,610,000) (Table 9). However, about the same proportion was noted when the red blood cells later rose to 4,600,000. The tendency for marked diurnal variation in the percentage of abnormally shaped red cells has been noted above and probably accounts for the variations noted at the different levels of red cell count. Beatrice and Irving, although presenting normal hemoglobin percentages and red blood cell counts, showed a moderate to marked ovalocytosis.

(f) *Control Studies of the Percentage of Oval and Elongated Red Blood Cells in a Miscellaneous Group of Patients.* Blood obtained from 135 unselected clinic and hospital patients (all white) was examined for the presence of oval and elongated cells. The customary fresh wet preparations were made and examined immediately and after 24 hours. In 3 instances, 3% of the red blood cells were oval and elongated; in 4 instances, 1% of the cells; in 11 instances, 0.25% to 0.5% of the cells; in 30, 0.1% to 0.2% of the cells were oval; while in 40, 1 abnormally shaped red blood cell per 1000 counted was found. In the remainder of the 47 patients no oval or elongated cells were noted. These results indicate that the presence of an occasional oval or elongated red blood cell may be of no significance.

Discussion. 1. REVIEW OF LITERATURE (WITH SPECIAL REFERENCE TO THE OCCURRENCE OF ELONGATED RED BLOOD CELLS IN THE WHITE RACE). The great majority of the cases of sickle-cell anemia and of cases showing sickled, elliptic and oval shaped red blood cells without anemia have been found to occur in the colored race. The literature has been well reviewed by Steinberg.³ That this disorder of the red blood cells occurs in individuals of the white race is still doubted by some who have written on the subject (Musser and Wintrobe⁴). However, several well-documented observations are now on record. Bishop,⁵ in 1914, described the occurrence in a white man and his sister of about 75% of oval shaped red blood cells. Four other members of this family had normal blood cells. Huck,^{6a} and Huck and Bigelow,^{6b} in 1923, made extensive studies of the effect of various substances upon the abnormal red blood cells found in 2 of 14 members of a white family. The 28-year-old patient and her mother each had 50% to 80% of oval red blood cells, but were otherwise in good physical condition and not anemic. Castana,⁷ in 1925, reported the first case (in an Italian child) of definite anemia with the presence of sickled red blood cells in an individual of the white race. No illustrations are, however, given and no mention is made of the behavior of the red blood cells in fresh "wet" preparations. Archibald,⁸ in 1926, described the occurrence of sickle-cell anemia in a 2-year-

old Arab child, a native of the African Sudan. The parents showed no sickled cells. This case, because of the definite possibility of racial admixture, should probably be excluded as a definite instance of the occurrence of sickle-cell anemia in the white race. The same holds true for Stewart's⁹ report (1927) of the occurrence of sickled cells in 2 Cuban children. Both of these children had definitely negroid facial characteristics, and the mother was probably a negress. The first case from Europe was reported, in 1928, by van den Bergh,¹⁰ who found 4 instances of elliptic red blood cells in a Dutch family. This was shortly followed by the reports of Bernhardt¹¹ and Günther¹² of German patients with the same disorder. Cooley and Lee,¹³ in 1929, reported a definite case of sickle-cell anemia in a Greek child, and in the same year Hunter and Adams¹⁴ observed in this country a Dutch family in which 3 generations presented elliptic red blood cells. Numerous relatives of this family were found by van den Bergh,¹⁵ in Holland, and the derivation of the elliptic red cells was finally traced to the third of 4 wives which the great-grandfather had married in Holland. The relatives of this third wife presented several instances of abnormally shaped erythrocytes. Sights and Simon,¹⁶ in 1931, reported a case of sickle-cell anemia in an American of Scotch-Irish parentage, and Rosenfeld and Pincus¹⁷ made careful studies of members of 3 generations of an Italian family who presented various degrees of sickling. Lawrence¹⁸ studied a number of patients and medical students in a university hospital and found several instances of sickling of the red blood cells. In 1931, the same author¹⁹ found oval red blood cells in 2 patients with pulmonary tuberculosis. One of these was Jewish and is thus the first representative of his race in whom sickled or oval red blood cells have been reported. Roth and Jung²⁰ found oval red blood cells in a white woman, aged 30 years. Cheney²¹ studied 81 members of an Italian family, 14 of whom showed oval-shaped red blood cells, and Grzegorzewski,²² in 1933, was also able to find 14 instances of the disorders in 5 generations of a white family living in Danzig.

2. THE TERMS SICKLE CELL, SICKLE-CELL ANEMIA, OVALOCYTOSIS, ETC. The terminology referring to these variations in the shape of the red blood cells has become greatly confused. The name "sickle-shaped red blood cells" given by Herrick,²³ in 1910, has been retained despite such suggestions as "drepanocytosis" (Hahn²⁴) and "meniscocytosis" (Graham and McCarty²⁴), etc.

"Latent sickling" (Emmel²⁵), "the sickle-cell trait," "latent sicklemia" are all terms indicating changes in the morphology of the red blood cells when blood is allowed to remain in wet preparations for 24 hours. "Sicklemia" refers to the presence of numbers of sickled red blood cells found at the moment blood is obtained. When anemia is also present, the condition is known as *sickle-cell anemia* (Mason,²⁶ 1922). "Ovalocytosis"^{11b} refers to blood in which,

although most of the red blood cells are elongated in one diameter, only an occasional one is bent in the characteristic sickle fashion.

Definite gradations in this type of abnormality of the red blood cells are thus seen to occur. These have been carefully studied by Günther¹² and Penati.²⁷ The slightest degree of abnormality is represented by the oval-shaped cells. When these occur in large numbers (10% of the red blood cells or greater), the term "ovalocytosis" may be used. The number of these cells in a wet preparation usually increases greatly on standing, and some of the cells become definitely elongated and frequently cigar or fusiform in shape. Elongation may thus be said to be the next degree of abnormality. The final and most marked stage, in which a banana or "sickle" shape is assumed, is called the "sickle cell." Although certain observers conclude that "ovalocytosis" and "sicklemia" are separate phenomena, it would appear unwise to differentiate sharply between them, since they may be closely related stages of the same general disturbance of the red blood cells.

3. RACIAL AND FAMILIAL CHARACTERISTICS. As noted above, most cases of oval and sickle-shaped red blood cells have been reported in the colored race. The occurrence of an instance of elongation in a white person, therefore, is always either doubted (Musser and Wintrobe⁴) or the question of racial admixture either recent or remote¹⁷ is entertained. The possibility of recent negroid admixture in our typically Jewish family, none of whom possessed any negroid characteristics whatsoever, is exceedingly remote. However, it must be admitted that the possibility of an admixture of negro blood in the distant past resulting in the transmission of a sickle-cell trait cannot certainly be excluded. This possibility may account for the occurrence of other cases in typically "white" individuals, although it must also be admitted that the sickle-cell trait may have been present for centuries in certain pure strains of white individuals.

The familial occurrence of this disorder is well known and needs no elaboration here. The exact mode of transmission, whether by male or female, and whether by a strictly Mendelian type of inheritance, has not yet been worked out.

4. PATHOGENESIS OF THE DISORDER. Race and heredity probably represent the greatest single factors in the occurrence of this disorder. There is no doubt, however, that the sickling trait may be modified *in vitro* by various mechanical and chemical factors. Hahn and Gillespie² emphasized the factor of anoxemia. Sriver and Waugh,²⁸ by altering the oxygen content of the forearm by means of a bandage, found that the degree of sickling varied directly with the decrease in oxygen tension. Sydenstricker,²⁹ however, found that the sickle cells in a case of sickle-cell anemia were unaffected by oxygen, and Graham and McCarty²⁴ failed to find an increase in the percentage of sickled red cells in blood removed from the heart under anaërobic conditions 27 hours after death.

Failure to change the shape of the red blood cells in our experiments by modifying the oxygen saturation of the blood in the circulation by either hyperoxygenation or anoxemia also serves to cast doubt upon the theory of anoxemia. Attempts to explain the elongation of the red blood cells by mechanical factors (pressure on the coverslip, etc.) have failed of proof. Auer,³⁰ in a recent study of the structure and function of filaments produced by living red corpuscles, concluded (on theoretical grounds) that "these filaments are probably the agents that cause cell deformity in sickle-cell anemia."

It is still not entirely certain whether the elongated red blood cells are produced as such in the bone marrow or whether their development takes place in the circulating blood. Several observers have made distinctly contradictory statements in regard to this question. Unfortunately, we were unable to study the bone marrow at biopsy in our cases. However, it was observed that the reticulocytes present were always round, and showed no tendency toward elongation of one of the diameters. This finding led to the speculation that it was only the more mature red blood cells which developed varying degrees of elongation and, therefore, that the phenomenon occurred in the circulating blood. Against this speculation, however, is the observation (questionable) by Roth and Jung²⁰ of oval red blood cells in the marrow.* The question as to whether the oval cells were in the marrow tissue or the circulating blood of the marrow would still remain open. Bernhardt,¹¹ in 1928, found that the bone marrow in a case of sickle-cell anemia had normal erythroblasts and normoblasts and concluded that the oval cells first appeared in the peripheral blood. That anemia does not of itself predispose to ovalocytosis is now definitely accepted. Conversely, the presence of large numbers of circulating ovalocytes does not predispose to anemia. Of 46 cases of ovalocytosis occurring in people of the white race, 37 were in good health and presented normal blood pictures. The others had slight degrees of hypochromic anemia probably associated with the various chronic diseases which were present.

The significance of the observations of the effect of various physical and chemical factors upon the red blood cells *in vitro* must to a certain degree be questioned. It cannot be denied that, although the red blood cells respond in various definite manners to various stimuli when studied outside the circulating blood, it is wholly improbable that striking changes either in pH, oxygen saturation, temperature, etc., occur within the body. These more or less artificial observations must be taken, therefore, as interesting

* Corrigan and Schiller,³¹ in a very recent communication, note that "a number of nucleated red cells appeared sickled" in the bone marrow from a case of sickle-cell anemia.

phenomena which may well have no reference to the underlying pathogenesis of the disorder. The most that can be said at present is that certain individuals have an hereditary tendency toward elongation of their red blood cells.

Summary. Large numbers of oval, elongated and sickled red blood cells were found in 3 members of a Jewish family, in whom no admixture of Negro blood could be elicited.

Studies of the effect upon these cells of time, temperature, pressure, Roentgen ray radiation, anticoagulants, various chemicals, certain gases and anemia were made.

The literature bearing on the occurrence of elongated and sickled red blood cells in individuals of the white race is reviewed.

It is probable that oval, elongated and sickled red cells and sickle-cell anemia represent various gradations in the same general abnormality of red blood cells. The significance of certain observations made upon the red cells *in vitro* is questioned.

The most important factor in the pathogenesis of the disorder appears to be that of heredity.

The appearance of oval, elongated and sickled red blood cells in members of the white race cannot longer be questioned.

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EXPERIMENTAL INTERFERENCE WITH CONDUCTION
IN THE HEART.

BY JANE SANDS ROBB, M.D., Sc.D., MARY EASBY, M.D.,

AND

J. G. FRED HISS, M.D.,

SYRACUSE, N. Y.

(From the Laboratory of Pharmacology, College of Medicine, Syracuse University.)

IN order that the problems of conduction in the heart may be solved, there must be no divorce between the facts of function and of structure. There is reason to suppose that theory has outrun observation and does not merit our full confidence, as the following citations imply.

There has been much inconsistency in the description of cardiac muscles (see Robb^{1,2,3} for extensive references), a confusion which perhaps influenced Lewis^{4,5} view, that they were without conduction significance. Unfamiliarity with the demarcation between adjacent muscles led to an easy acceptance of this opinion.

The statement that heart muscle forms a syncytium is only a partial truth. Pettigrew⁶ quotes unpublished work of his students confirming their observation that when the muscle layers are separated, one from another, no muscle fibers are cut, only connective tissue strands being broken. (See also Robb.¹) Pettigrew also examined microscopic preparations to confirm the gross observation. One must then limit the statement that "the cardiac muscle forms a syncytium" to mean that *within any given muscle bundle the fibers form a syncytium*. Thus, there is not a syncytial muscular connection between any two muscle bundles, *e. g.*, the superficial and deep sinospirals. The one overlies the other in areas, but the two are ever separated by connective tissue septa in which are found the bloodvessels. Various textbooks of histology will support this statement (*e. g.*, Fig. 172, Lewis and Stöhr). The physiologic implication is that excitation would doubtless take the path of least resistance, *i. e.*, along the syncytium of a given muscle, rather than cross the connective tissue barrier from one muscle to another. Direct linear distances, disregarding muscle boundaries, were used in the calculation of conduction rates.

The blood supply to the ventricles has been admirably described by Gross,⁷ and further details have been added by Wearn.⁸ However, the specific blood supply to the individual muscle bundles has been uninvestigated. In such a study, presently to appear, each muscle is found to have a fairly precise blood supply (Robb). Ligation of a definite branch of the coronary system will consistently cause anemia in a specific portion of a given muscle. The fact that

one may limit an infarct to a single muscle makes the study of conduction less complicated.

Knowledge of the actual distribution of the conducting system in the heart still awaits final evaluation. The classical description recognizes a sinoauricular node (an isolated structure), the auriculo-ventricular node of Tawara, the bundle of His, right and left branches of the bundle and subendocardial Purkinje ramifications. The studies of Keith,⁹ Kent,¹⁰ Curran,¹¹ Todd,¹² Taussig,¹³ and Abramson and Cardwell^{14,15} all suggest the possibility of a more general distribution in mammals, including man. The Purkinje system unquestionably ramifies through the heart substance in ruminants, and perhaps in all mammals, even connecting the two ventricles; also multiple muscular connections between auricle and ventricle have been supported.

A further assumption is commonly made by physiologists, namely, that a stimulus applied to the surface of the heart has to pass through muscle tissue only. On this basis, two types of conduction were inferred—one of 400 mm./sec. for ventricular muscle, and another approximating 5000 mm./sec. for Purkinje substance. In the light of the histologic data referred to above—particularly that of Todd and Abramson, this assumption, and hence the conclusion as to two conduction rates, is open to suspicion. The apparent differences in conduction rate may be only a question of the length of the pathway actually involved.

Because these facts regarding the gross anatomy, the blood supply and the distribution of the Purkinje tissue to the ventricular muscle bundles have not been taken into sufficient account by the physiologists in the present theory of conduction in the ventricle, it seems obvious that it should not merit great confidence.

Experimental Methods. Various methods may be employed to study conduction in the ventricle. A technique hitherto untried is the elimination of muscle bundles, one at a time, by appropriate vessel ligation, and observation of resultant change in the electrocardiogram. The author^{17,18} has reported elsewhere two such studies. It is also important to repeat the classical procedures of Lewis, having due regard to the anatomic facts stressed above. This paper is concerned with a repetition of two such experiments.

On dogs anesthetized with chlorotone (0.25 gm./kg., 1st series) or with pentobarbital (50 mg./kg., 2d series), the thorax was opened, the heart exposed and the pericardium stitched to the edges of the wound. In the 1st series there were attached directly to the heart electrodes of glass tubes having a gelatin-saline plug in which was embedded a thick silver wire coated with silver chlorid. A small amount of absorbent cotton was inserted into the gelatin at the tip of each tube, and this cotton wick, wet with 0.9% saline, was attached to the heart by a single superficial stitch. This ensured a constant contact and yet allowed for free movement of the ventricle. Such electrodes are strictly non-polarizable and have a resistance of 500 Ohms or less. All records were taken with standard electrocardiographic technique. A total of 66 muscle studies have been made on 21 dogs.

*Series I.** One of the experiments upon which Lewis' theory of conduction in the ventricle depends is that of attaching two direct electrodes to the surface of the heart and subsequently making a cut between them. Lewis found that this procedure did not alter the conduction time from one electrode to the other.

In Fig. 1 are shown typical data obtained upon repeating this experiment. The small insert, at the left, is reproduced from Lewis,⁵ and shows where his electrodes were placed. If the experiment is repeated with the electrodes in that position, Lewis' observation is confirmed. The corresponding insert (*F*) is a reproduction from Mall¹⁹ and shows the direction of fibers on the surface of the heart. It is obvious that a cut in the position made by Lewis only separated the fibers in the syncytium. If the experiment is modified so that the electrodes are placed as in the lower insert on the right (*G*), that is, in such a position that the fibers are cut transversely, then a marked change in the electrocardiogram appears. This alteration is observed in "natural" as well as in "excited" beats. The contour of the *Q-R-S* complex is altered and the duration increased subsequent to the cut. Attention is called to the fact that not only are the contour and time relations of the direct leads altered, but similar changes are to be seen in the indirect leads. Also, one notices in tracing *A*² that the mere attachment of the direct electrodes to the surface of the heart has elevated the *R-T* segment and that subsequent to the cutting this segment is still further raised. (Randles, Gorham and Dresbach.²²)

Series II.† In Fig. 2 is shown a diagrammatic representation of the superficial sinospiral muscle. At the point marked "1" the muscle is of small compass. The blood supply to the internal portion (anterior papillary muscle) is derived from branches of the left anterior descending branch of the left coronary artery and can easily be identified and ligated. Rendering the internal portion of this muscle anemic causes an elevation of *R-T* in all leads (Fig. 3, 3; also Robb¹⁷).

If in addition to this lesion one makes a cut transverse to the muscle fibers proximal to the ligation, in the position marked "2," no further change occurs (Fig. 3, 4).

A branch of the left fork of the bundle of His enters this muscle near its mitral insertion. We were able to introduce an instrument through the left auricular appendage into the left ventricle, where cuts were made on the anterior papillary muscle, thus breaking its connection to the bundle of His. The same type of electrocardiogram is obtained (compare Fig. 3, 4 and 5), the only additional change found being the complete loss of the negative *S* wave.

* These experiments were performed with the help of Dr. Easby and with equipment supplied by the Laboratory of Physiology, University of Pennsylvania and by the Philadelphia General Hospital.

† Experiments performed with the aid of Dr. J. G. Fred Hiss—some in the Laboratory of Physiology, School of Medicine, Rochester University.

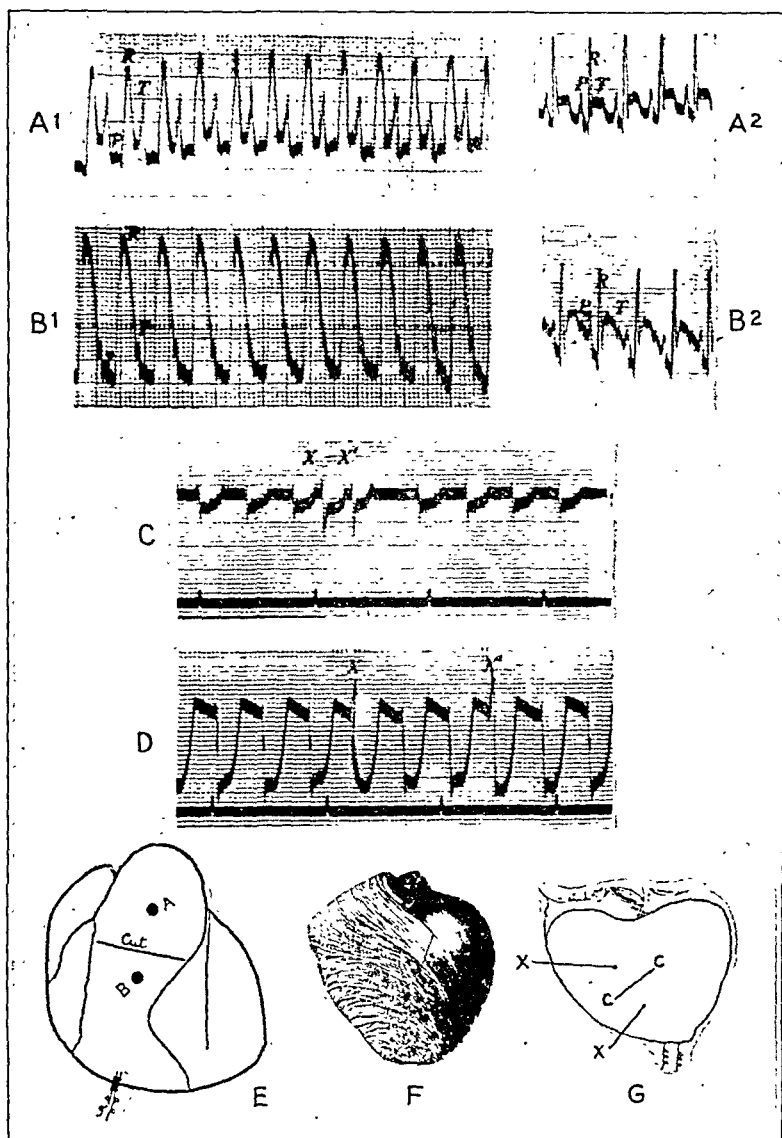


FIG. 1.—A¹, Electrocardiogram with direct contacts placed at points $x-x^1$ on the heart (as in insert G). Time intervals are $\frac{1}{3}$ second each. A², Simultaneous Lead 2, for additional "control." B¹—B², Records from above leads taken after cutting the muscle transversely between the take-offs (cut shown as line $c-c$ in insert G), each differing from control above it. C, Direct leads from another muscle on the surface of the same heart, showing two excited beats. D, Same leads, after transverse section of the muscle between. Note that both normal and excited beats are altered and prolonged. E, Diagram from Lewis, showing the position of electrodes and the direction of the "cut" in his experiment. F, Drawing by Mall, showing diagonal course of surface muscles, indicating that Lewis did not have his two leads on the same bundle and that he did not completely transect any bundle. G, Location of leads at $x-x^1$ in our experiment.

These data indicate that in the superficial sinospiral muscle, *if an initial lesion involves the entire cross section of the muscle at the apex*, a further lesion of the uninjured portion of the muscle will not cause a further change in the electrocardiogram.

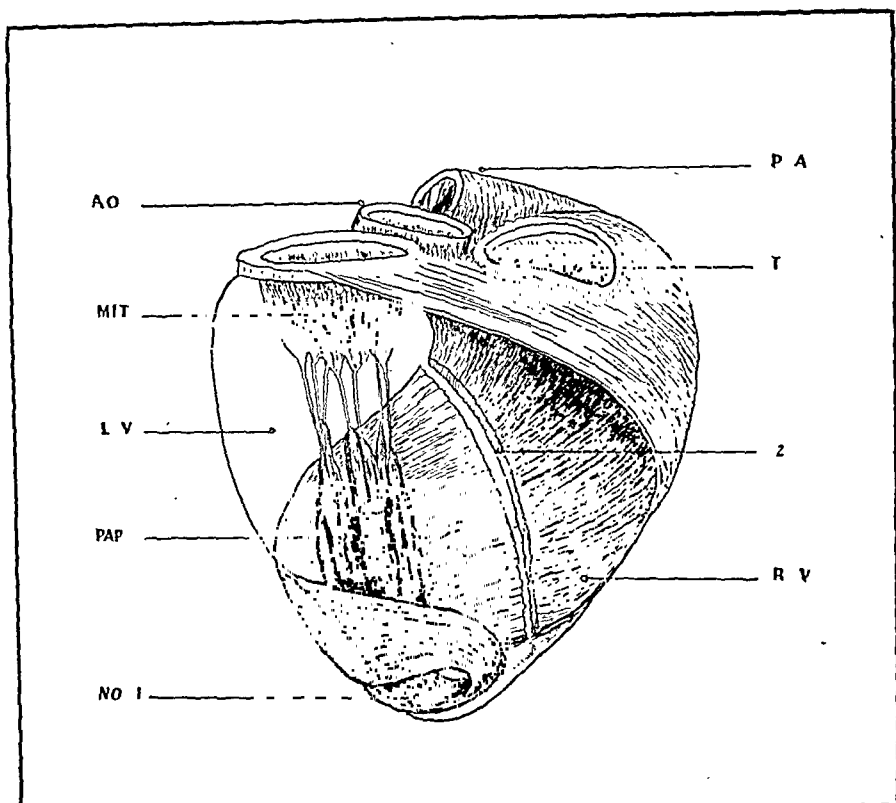


FIG. 2.—Posterior view of the superficial sinospiral muscle. AO, Aorta; MIT, mitral valve; L V, left ventricle; PAP, anterior papillary muscle; P A, pulmonary artery; T, tricuspid opening; R V, right ventricle. No. 1, Locus of apex muscle lesion, by local vessel ligation, thus rendering anemic the central portion of this muscle. No. 2, Locus of subsequent lesion, by transection, which initiates no further modification of the E.C.G.

Discussion.—This observation is hard to explain if one accepts the theory of radial penetration of the excitation through the thickness of the walls of the ventricles. If this radial penetration were a fact, one would expect that even though the apex of the superficial sinospiral were injured, a lesion in its course over the external surface of the ventricle would produce a further electrical change. Recently Hill²⁰ has suggested that the immediate effect of coronary thrombosis upon the electrocardiogram is due to an injury current. If this were the only explanation, then a second injury should cause an increased effect, which is not the case in this experiment. On the other hand, if conduction in the ventricle is not radial, but is parallel to the direction of the muscle fibers of

each muscle bundle, then one would expect that the lesion at the apex would produce the total change possible and that further lesions in portions of the muscle where the blood supply is intact would have no effect.

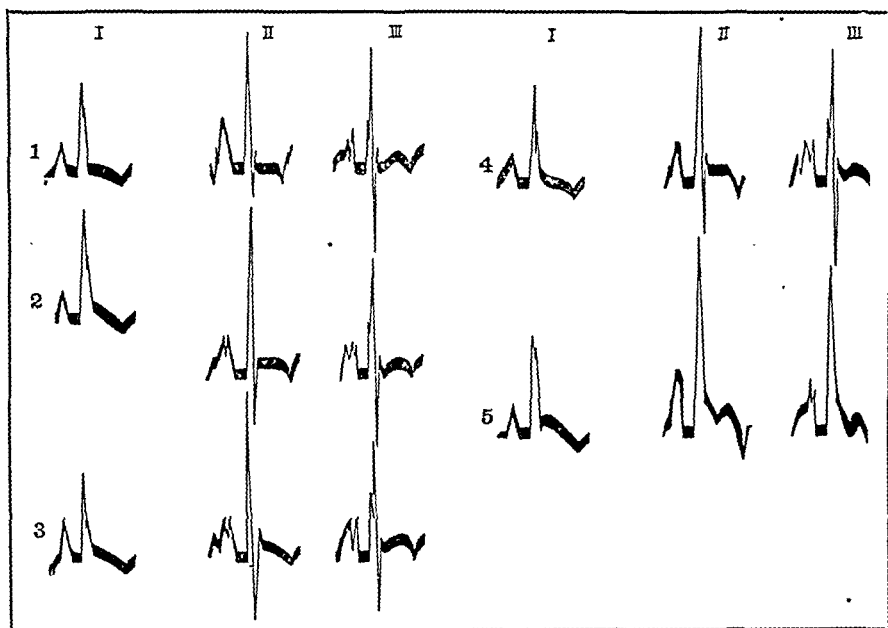


FIG. 3.—Three standard leads showing the successive effects of several procedures on the superficial sinospiral muscle in a single heart. 1, Control with heart exposed; 2, control with compression of a few muscle fibers; 3, apex blood supply ligated (Fig. 2); 4, transverse cut of muscle; 5, interruption of the main Purkinje branches to this muscle.

Lewis⁴ considered the possibility of conduction by way of the muscle bands and decided against this interpretation. The estimation of conduction rates in the ventricle, upon which his theory is based, is made only from the excited beats, and some of these rates are excluded. The more rapid rates of 1200 to 1500 mm. per second were found over the right ventricle, where he believed the conduction was through the Purkinje substance. The slower rates were obtained from the left ventricle, where he assumed only muscle tissue was involved. The work of Todd¹² and Abramson¹⁵ shows that this assumption is unwarranted, for the Purkinje fibers ramify throughout the muscle of the left ventricle as well as that of the right. Lewis⁴ gives data for transmission with leads parallel to the fibers and transverse to the fibers for both natural and excited beats. The rate for transverse conduction is slower both in excited and in natural beats. These differences in conduction deserve more emphasis than was originally given them. Such data would support the opinion that conduction is along the direction of the muscle bundles.

Wiggers,²¹ studying the response of the mammalian ventricle to surface stimuli, found that the "pressure maximum" of beats excited at the surface was always less than that of normal beats. In explaining the results of his study, he suggests (p. 376): "While this double contraction process also contributes to the decrease in total tension developed, evidence is cited that this is further influenced by the abnormal directional spread of impulses over the conducting system. *Such changes in distribution (Fig. 4) may alter the order in which the muscle scrolls are excited* (italics by author) and this in turn may affect the effectiveness of contraction of the entire ventricle as gauged by tension development. If there were "radial" penetration, the order of the involvement of the scrolls should be unimportant.

The consistency of results obtained in these experiments suggest that at autopsy, in order to correlate pathology with clinical evidence, lesions should be described with reference to the component muscles of the ventricle rather than located topographically.

Conclusions. 1. If the fibers of a ventricular muscle are cut transversely a characteristic change in the form and in the time relations of the electrocardiogram result.

2. Electrocardiograms of muscle lesions are of the "coronary" type.

3. Various types of injury to a given muscle, such as compression of the tissue, interruption of the blood supply, cutting the band transversely, or intraventricular interruption of the Purkinje supply to the muscle, all produce a result typical for that muscle.

4. Data accumulating suggest that impulse conduction is parallel to the direction of fibers of the ventricular muscle bands.

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CLINICAL SIGNIFICANCE OF THE M OR W SHAPED Q-R-S COMPLEX IN LEAD II OF THE ELECTROCARDIOGRAM.

BY JOSEPH EDEIKEN, M.D.,

INSTRUCTOR IN MEDICINE, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,
AND

CHARLES C. WOLFERTH, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, SCHOOL OF MEDICINE, UNIVERSITY OF
PENNSYLVANIA, PHILADELPHIA, PA.

(From the Robinette Foundation, Medical Clinic, Hospital of the University of
Pennsylvania.)

A SEARCH of the literature regarding the significance of *M* and *W* shaped *Q-R-S* complexes of low amplitude in Lead II of the electrocardiogram failed to yield any information on the subject. Our attention had been directed to complexes of this type because of the presence of a *W* wave in Lead II of the electrocardiogram obtained from a patient with probable coronary occlusion. At the time, no significance could be attached to this finding although it was the only definite abnormality noted; subsequent observations, however, indicated its importance.

The present report deals with *Q-R-S* complexes in Lead II having the following characteristics:

1. The amplitude does not exceed 5 mm.
2. The complex is definitely *M* or *W* shaped throughout the tracing.
3. All the components of the complex are above the base line in the *M* shaped complexes, and below the base line in the *W* shaped complexes.
4. Occasionally there is a deflection either preceding or following the *M* or *W* shaped part of the complex, opposite in direction to its associated *M* or *W* shaped component.
5. The duration of the *M* or *W* shaped part of the complex is at least 0.08 sec. (Fig. 1, *A* and *B*).

Complexes bearing certain resemblances to the above but excluded from this group are shown in Fig. 2. Their possible relationship

to the complexes under consideration is discussed later in connection with changes in form of these complexes.

The material is, for the most part, the same as that used in the study of the significant Q III wave.¹ It is arbitrarily divided into six groups: I, 960 college students with presumably normal cardiovascular systems;* II, 117 college athletes;* III, 145 railroad executives; IV, 116 cases with the anginal syndrome; V, 4450 electrocardiograms taken in the years 1927 to August, 1932 inclusive; VI, 25 cases with *M* or *W* waves not included in the above groups.

There is no overlapping in Groups I, II and VI. Cases in Groups III and IV which happened to be studied within the time limit of Group V are included in that group.

GROUPS I, II and III. There was no instance of an *M* or *W* complex, which completely satisfied the criteria stated above.

GROUP IV. There were 5 records showing this complex. Two of these patients died following coronary occlusion during their stay in the hospital; 2 gave a history suggestive of a coronary occlusion; of these 1 has since died and the other is incapacitated because of pain on effort. The 5th patient died suddenly (Fig. 3).

A significant Q III wave was the only other electrocardiographic abnormality noted in 1 case; 1 showed a flat *T* wave in Lead II and in 1 a low *T*-2 was associated with a significant Q III. Two showed *T* wave inversion and slurred Q-R-S complexes.

GROUP V. In Group V there were 21 records showing this complex in Lead II, including the 5 in Group IV. The diagnoses† made in the 16 remaining cases are as follows: Cerebral thrombosis 1, myocardial disease with decompensation 4, coronary occlusion 3, rheumatic heart disease 1, syphilitic cardiovascular disease 3, hypertension and/or arteriosclerosis 3, unknown 1. The patient who had cerebral thrombosis cannot be traced. Of these 16, 10 are dead, 5 are more or less incapacitated (and from the clinical findings appear to have a poor prognosis). One patient is comparatively free of symptoms but has bundle-branch block. Only 1 of the 10 fatal cases lived more than 2 years after the taking of the electrocardiogram showing an *M* or *W* wave. This patient suffered from a coronary occlusion in 1925. At that time the electrocardiogram was abnormal but an *M* or *W* complex was not present in Lead II. In April, 1927, his electrocardiogram showed an *M* complex in Lead II; death from cardiac decompensation occurred in June, 1929. In 4 instances death took place within 6 months and 1 of these fatalities occurred on the operating table. The patient, a man aged 50, had complained of upper right abdominal pain and had symptoms suggestive of cholecystitis. At operation, however, a

* These tracings were made available through the courtesy of Dr. Francis C. Wood.

† The diagnoses given are those of the hospital records. In some, the history suggested a coronary occlusion but sufficient data were not present to warrant a definite diagnosis.

normal gall bladder was found and no abnormal condition sufficient to explain his symptoms was disclosed. While the abdomen was being closed, the patient suddenly died. Postmortem examination was not permitted. In reviewing the history and clinical and laboratory findings of this patient, the *M* wave in Lead II was the principal finding which would point to the heart as the cause of his symptoms. Although there is no proof that a cardiac accident was responsible for his death, its suddenness and the lack of any other explanation suggested this possibility.

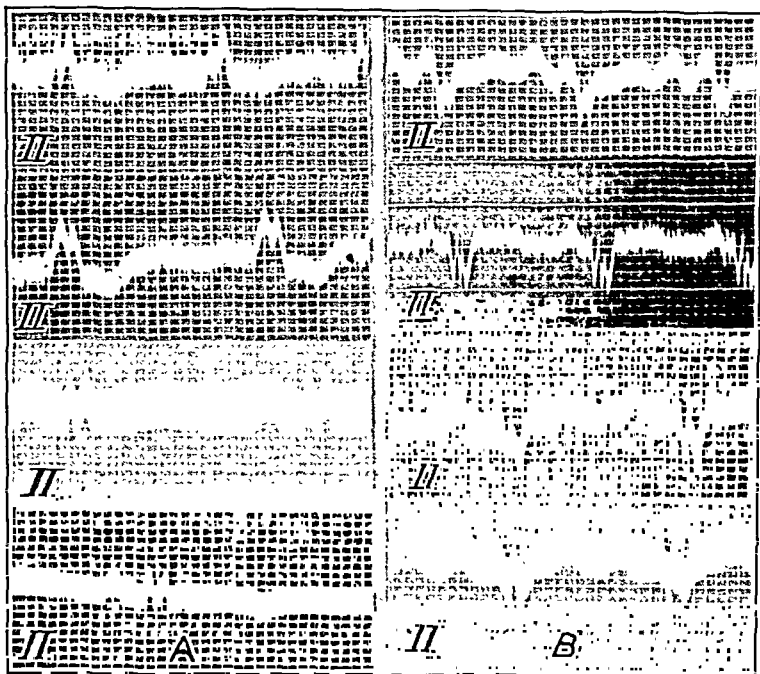


FIG. 1.—A, Lead II of four records, showing *M* type of *Q-R-S* complex. B, Lead II of four records showing *W* type of *Q-R-S* complex. Note splitting of middle limb in second tracing.

Four of the 5 patients who are known to be alive were first observed during the year preceding the study of this group. The 5th patient had coronary occlusion in 1927 from which he recovered, although he is more or less incapacitated.

Among the 16 cases, the electrocardiogram showed no definite abnormality in 1 instance, except for the *M* or *W* wave; 1 record showed a flat *T* wave in Lead I; the *T* waves were inverted in 2 leads in 5 cases; 4 showed inversion of *T* waves and slurred *Q-R-S* complexes. There were 4 records showing bundle-branch block and 1 of complete block.*

* The electrocardiograms of the 5 patients who were alive are all abnormal—2 show bundle-branch block, 1 complete *A-V* dissociation and the other 2 marked *Q-R-S* changes and *T* wave inversion following coronary occlusion.

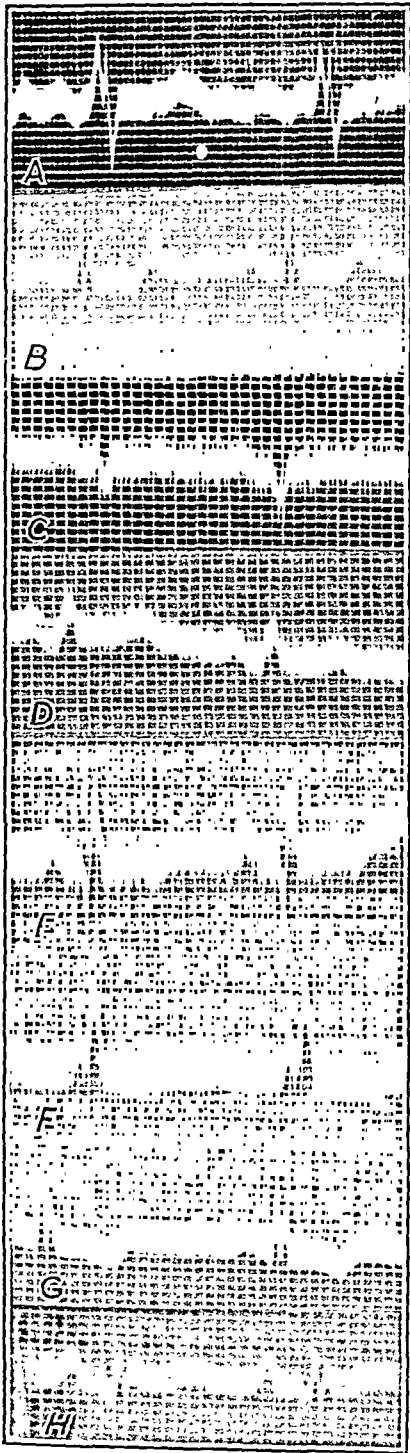


FIG. 2.—Lead II of eight records in which Q-R-S complex simulates M or W type of complex.

GROUP VI. In this group are 25 records showing an *M* or *W* wave but not included in any of the above groups. All were taken within the past 2 years. Twenty cases were diagnosed clinically as having coronary occlusion. In Figs. 4 and 5 are the electrocardiograms of 2 of these cases taken before and after the occlusion. The 21st case gave a history of attacks of substernal pain but died following an embolus which occluded the aorta at its bifurcation. At postmortem the heart muscle was found "pale, grayish, and extremely friable." No evidences of an old or recent coronary occlusion was found. Another case was that of a man aged 61,

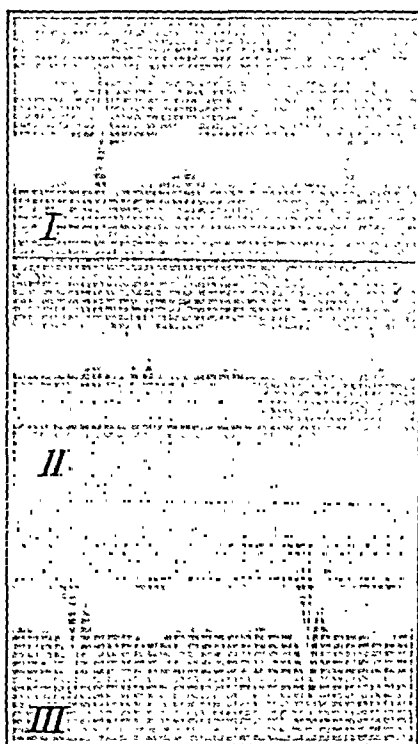


FIG. 3.—*M* shape *Q-R-S* complex in electrocardiogram of man with anginal syndrome. Death was sudden.

with syphilitic cardiovascular disease. Another patient had hypertension with blood pressure figures averaging about 230/130.

The 24th and 25th cases are obscure and have recently come to our attention. A young woman, aged 20, had vague complaints referable to the gastro-intestinal tract. An enlarged heart was discovered during routine examination. Auscultation revealed a third sound falling in early diastole over the body of the heart; the significance of which was in doubt, although the majority of observers regarded it as the opening snap of mitral stenosis. The electrocardiogram and orthodiagram are seen in Figure VI. No definite

diagnosis has been made but there can be little doubt that the heart is abnormal. The age of the patient, the lack of cardiac symptoms, the insignificant past medical history, and the large abnormally shaped heart suggest the possibility of a congenital lesion.

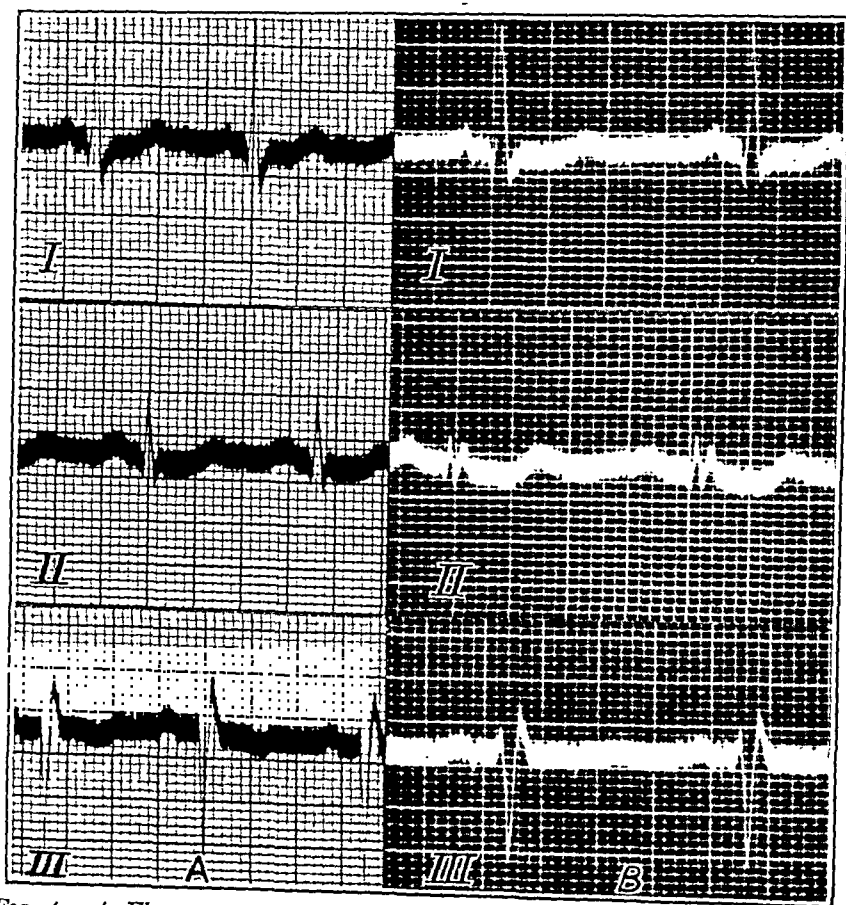


FIG. 4.—A, Electrocardiogram of man, aged 50. B, Electrocardiogram of same patient taken after possible coronary occlusion and about 2 years after A. Death occurred within a year after taking of B.

The 25th case was a man aged 35 who complained of palpitation and for no apparent reason was tired and exhausted toward evening. Examination failed to disclose any cardiovascular abnormality although the electrocardiogram showed low and slurred Q-R-S complexes in all leads and an M wave in Lead II. His symptoms improved and several months later his electrocardiogram failed to show the M wave.*

* In several cases of coronary occlusion the M and W wave in subsequent electrocardiograms have been replaced by complexes similar to those in Fig. 2. It is, therefore, probable that many cases showing a notched or split Q-R-S-2 have at some time after the occlusion shown an M or W wave in Lead II.

. Nine of the 25 patients in this group are dead but it is of interest that 14 of the 16 alive were first observed during the past year and 13 of these 14 have had coronary occlusion. The remaining 2 cases are the obscure cases described above. In almost all the cases with

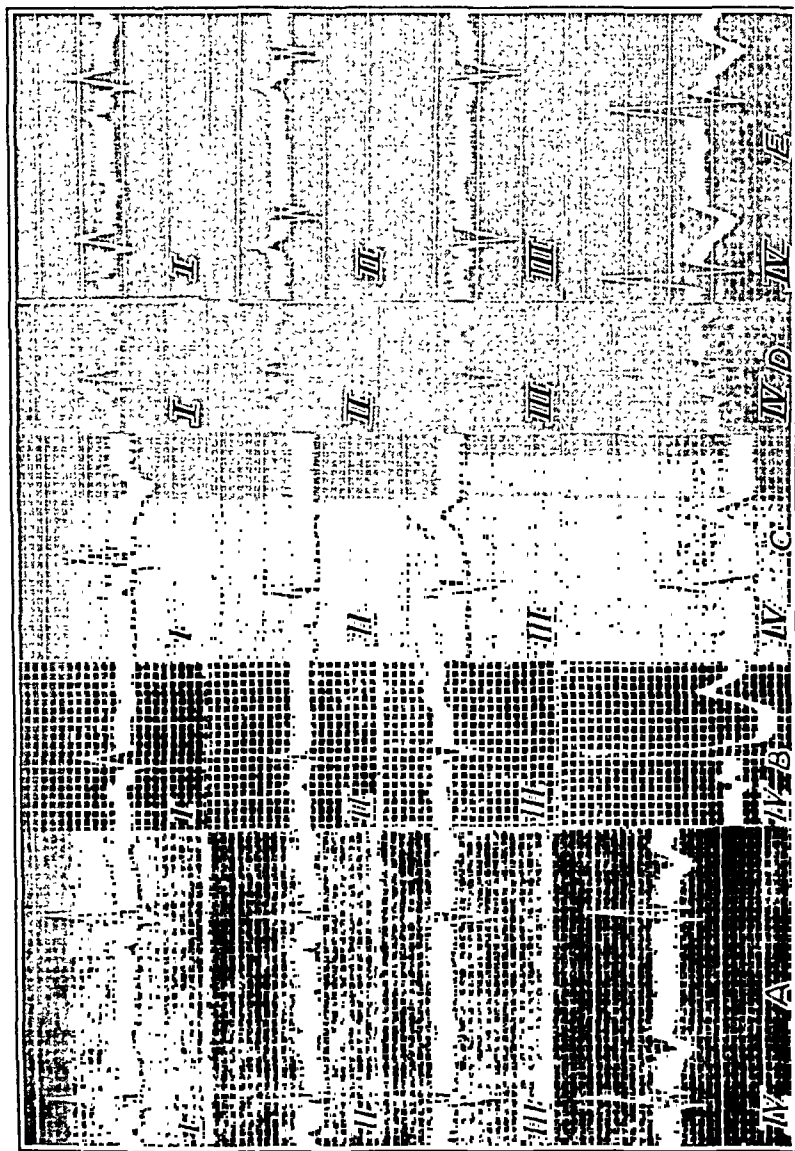


FIG. 5.—4, Electrocardiogram of man, aged 58, with anginal syndrome. B, 1 week after occlusion. C, 7 weeks later. D, 2 days after second occlusion and 13 months after C. E, 9 weeks later, showing formation of W wave in Lead II.

coronary occlusion, the *M* and *W* waves were observed 4 weeks or more after the occlusion. However, in several cases it has been observed immediately after.

In no case of this group showing *M* or *W* waves could the electrocardiogram be considered normal in other respects. However,

in 11, the other changes were either slight or inconclusive. In 1 case a significant *Q*-III wave was the only abnormality noted; another showed low *Q*-*R*-*S* complexes; in 2 cases the *Q*-*R*-*S* com-

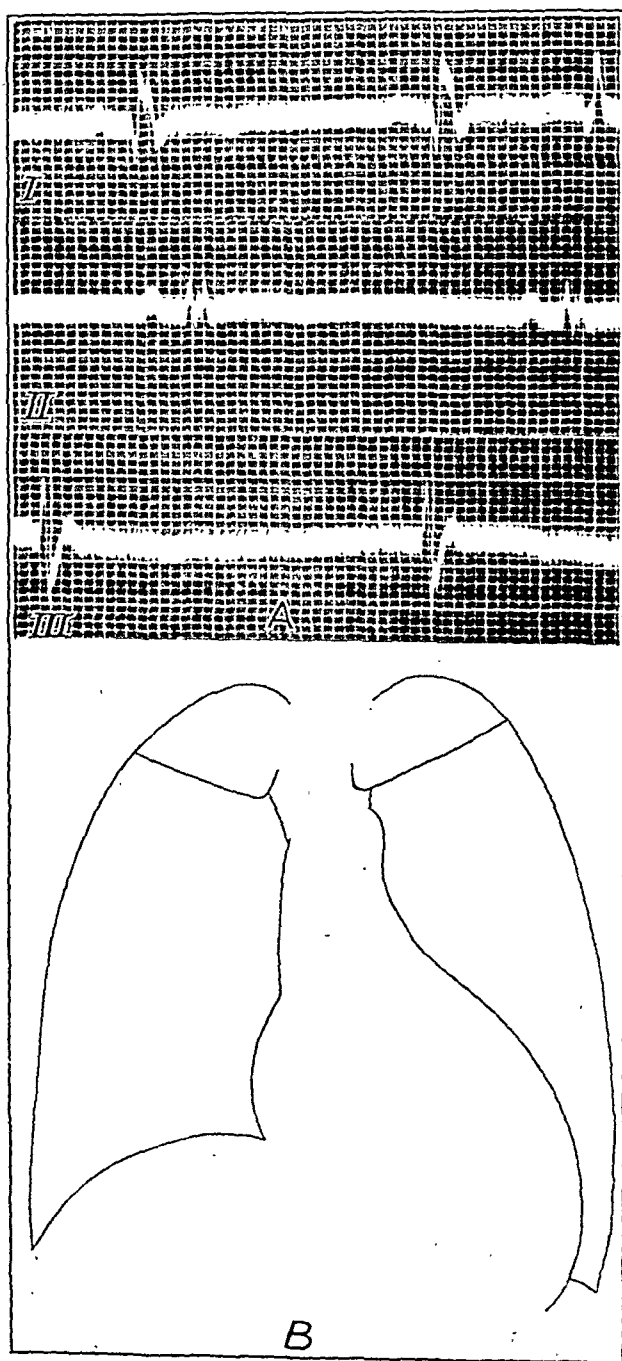


FIG. 6.—A, Electrocardiogram of young woman, aged 20, showing *M* wave in Lead II. There are no complaints referable to the cardiovascular system. Diagnosis obscure. B, Orthodiagram of same patient.

plexes were somewhat slurred; 1 case showed a Q - R - S complex of 0.11 second; in 3 cases T was upright but of low amplitude; 1 tracing showed the S - T interval raised (1.5 mm.) in Leads II and III; in 1 instance the record showed a flat T -2, an inverted T -3 and

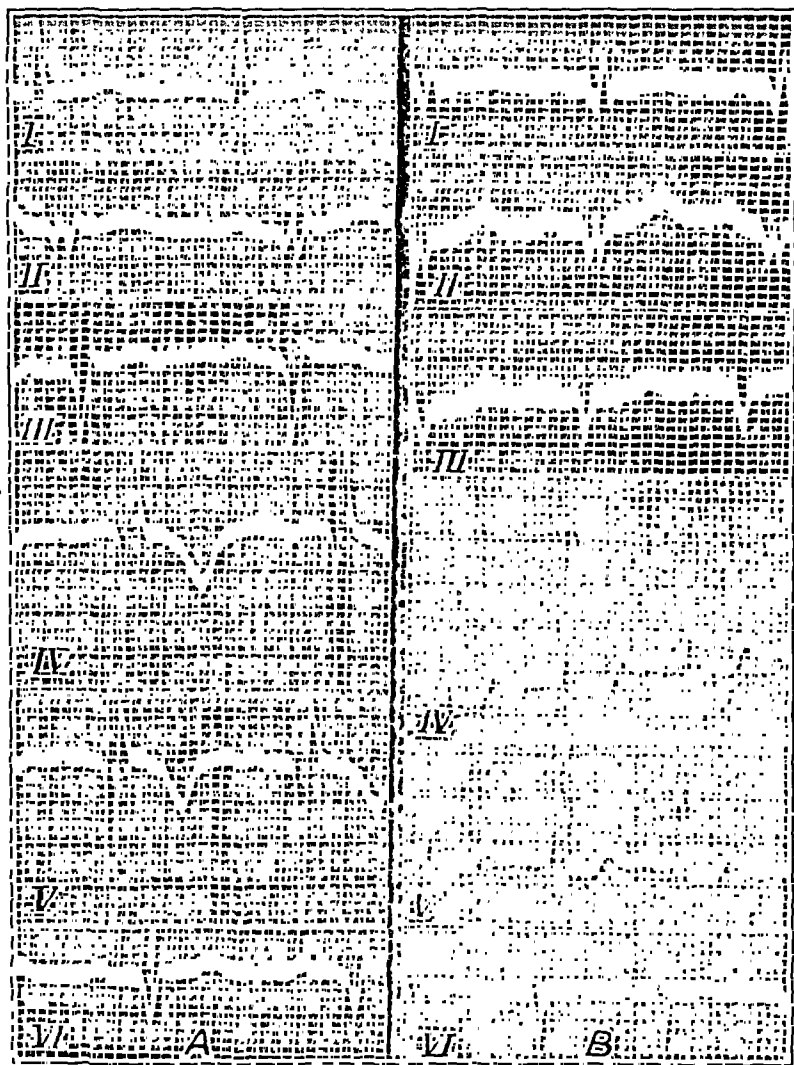


FIG. 7.—*A*, Electrocardiogram of man, aged 49, who has recovered from a suspected occlusion of the right coronary artery. Chest leads are normal. *B*, Electrocardiogram of man, aged 59, who has recovered from a suspected occlusion of the left coronary artery.

numerous ventricular extrasystoles; another case showed a Q -III wave and a Q - R - S complex of 0.11 second. The remaining 14 cases showed various T wave and Q - R - S complex changes indicative of severe myocardial disease.

Discussion. The infrequency of an *M* or *W* wave in electrocardiograms of individuals with presumably normal hearts and conversely the finding of cardiac damage in a vast majority of cases in whom the electrocardiogram shows this wave, suggests its importance.

Of the 46 records showing an *M* or *W* wave 28 were from patients suspected of coronary occlusion and the histories of some of the remainder also suggested coronary occlusion but sufficient evidence was not present to warrant a definite diagnosis. The latter were divided as follows: Cardiovascular syphilis, 4; hypertension and/or

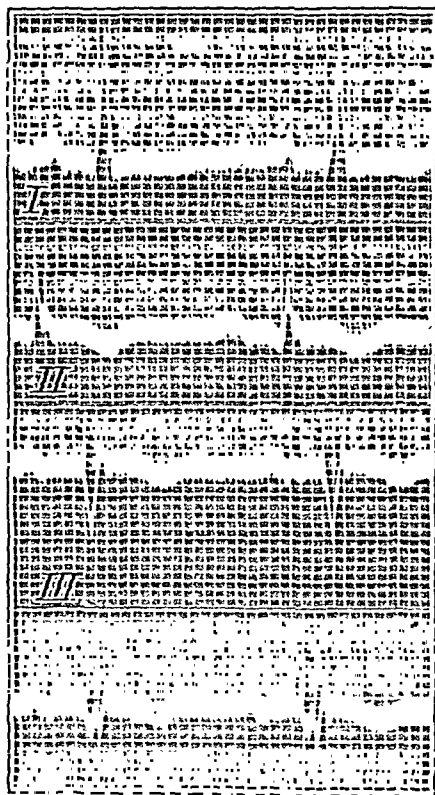


FIG. 8.—Electrocardiogram of man, aged 64, who had recovered from occlusion of right coronary artery; *W* wave in unconventional lead (right arm electrode at angle of scapula and left leg electrode in place).

arteriosclerosis, 4; myocardial disease—etiology unknown, 4; rheumatic heart disease, 1; cerebral thrombosis, 1; unknown, 4.

A study of the cases showing an *M* or *W* wave suggests that an intraventricular conduction abnormality as a result of myocardial disease is responsible for its production in most cases. Its comparative frequency in cases of coronary occlusion and in patients whose electrocardiograms show bundle-branch block supports this view. Unfortunately necropsy was performed in only 3 cases as nearly all of the patients died outside of the hospital, but in the 3 cases, myocardial damage was extensive.

From the electrocardiographic point of view, tracings showing an *M* or *W* shaped *Q-R-S* complex in Lead II can be divided into two groups: (1) those showing other abnormalities which have proven of prognostic significance, such as inverted *T* waves, bundle-branch block and complete heart block; (2) those records either not showing other definite abnormalities or in which the changes from the normal were not great.

The prognostic significance of electrocardiograms showing inverted *T* waves in the various leads, bundle-branch block and complete heart block has been established. Of the 46 tracings showing an *M* or *W* complex in Lead II, 30 belong to this group and it is doubtful whether the *M* or *W* complex adds to their prognostic significance. However, the fact that the majority of records showing an *M* or *W* wave in Lead II are from patients who have had coronary occlusion, may, in certain cases showing atypical electrocardiograms, be an aid in diagnosis. This is especially true in cases of right coronary artery occlusion in whom the chest leads are sometimes normal and also in the chronic stages of the disease during which the electrocardiographic changes may not be characteristic (Fig. 7, *A* and *B*).

However, the importance of the *M* or *W* complex must be determined by study of patients whose tracings are otherwise within normal limits or show only minor changes to which serious prognostic significance cannot properly be attributed. Of the 16 cases in this group 1 showed no definite abnormality, 5 had low (but not inverted) *T* waves in a single lead; 2, significant *Q*-III waves, and 1 showed a significant *Q*-III wave associated with a low but upright *T*-2, and 1 showed low *Q-R-S* complexes. Two cases showed slight slurring of the *Q-R-S* complexes, 1 slight elevation of the *S-T* interval, 2 showed a *Q-R-S* complex of 0.11 second, 1 of which was associated with a *Q*-III wave and 1 had a flat *T*-2, inverted *T*-3 and numerous ventricular extrasystoles. Eight of the above 16 patients died within a period of 2 years after the *M* or *W* complex was first observed; 1 patient has survived 5 years but is incapacitated because of pain on effort. The remainder, including the case with apparently no cardiovascular disease, have recently come under observation.

From the diagnostic point of view, Group VI is the most important. The patients have been more thoroughly studied and in a number, chest leads have been taken in an attempt to arrive at a more definite diagnosis. The frequency of coronary occlusion (80%) in this group is sufficiently great to suggest that these waves have some diagnostic value, their relative frequency exceeding that of the significant *Q*-III in the anginal syndrome as noted by various studies: Pardee 63%,² Willius³ 38%, Zisken⁴ 14%, Strauss and Feldman⁵ 16%, France⁶ 45%, Edeiken and Wolferth¹ 29%. When significant *Q*-III waves follow coronary occlusion they indicate infarction in

or near the posterior part of the interventricular septum. On the other hand, *M* or *W* waves may be associated with either anterior or posterior infarction.

The electrocardiograms of many of the patients with coronary occlusion were first taken after the occlusion occurred and it is therefore impossible to state whether the *M* or *W* wave preceded or was the result of the infarction.

However, in 2 cases (Figs. 4 and 5) in which the electrocardiograms were taken before and after coronary occlusion, the *M* or *W* wave followed the occlusion and in 1 of these cases it appeared only after the second occlusion. In 2 other cases in which electrocardiograms were taken at intervals after the occlusion, a *W* wave appeared after 6 weeks in 1, and 3 months in the other. In both cases it was not present in earlier or later electrocardiograms.

The *M* and *W* waves are not, therefore, in all cases permanent changes and it is possible that some of the tracings in which *Q-R-S* complexes in Lead II resemble the *M* or *W*, but are not included because they do not conform to the criteria stated (Fig. 2), may also be of equal significance, since one electrocardiogram may show one of these types of *Q-R-S* complexes whereas another taken at a later date may show the other type of coronary occlusion.

It is also probable that a change in electrical axis may cause some complexes of the type shown in Fig. 2 to assume an *M* or *W* form. Two cases, not included in this study, showed a slurred *Q-R-S* complex in Lead II which was very suggestive of an *M* wave in several complexes. In an unconventional lead, however, (right arm electrode at angle of left scapula and left leg electrode in place) an *M* or *W* wave was present throughout the tracing (Fig. 8). Both cases had a history of coronary occlusion; 1 patient is alive, the other died of pneumonia. However, the unconventional lead employed in these 2 cases has an axis about midway between Lead II and III and, although the *M* or *W* wave in these two instances appears significant, it is obvious that conclusions cannot be drawn from the findings in 2 isolated cases.

Complexes of the *M* or *W* type occur frequently in Lead III and occasionally in Lead I. Although certain cases with undoubted coronary occlusion have shown an *M* or *W* wave in Lead III, complexes of this description are seen in tracings from presumably normal individuals.

Three instances of the *M* or *W* complex occurring in Lead I have been observed in this study. Two of these patients had suffered from a coronary occlusion; 1 died 6 weeks after the tracing was taken, the second is incapacitated because of pain on effort and the third suffered from rheumatic heart disease with mitral stenosis and regurgitation. Death occurred as the result of a pulmonary embolism 11 days after the taking of the tracing.

Summary and Conclusions. 1. An *M* or *W* wave in Lead II of the electrocardiogram having the characteristics defined in this paper has *not* been observed in tracings of 1077 presumably normal adults.

2. It was seen 5 times (4.3%) in 116 patients with the anginal syndrome. After a period of 3 years, 4 of the 5 are dead, the other incapacitated.

3. In 4450 unselected electrocardiograms of hospital and clinic patients, the *M* or *W* wave was seen in 21 tracings (0.47%). Of these patients 14 are dead, and 6 show clinical evidence of severe myocardial disease; 1 cannot be traced. The electrocardiograms of 2 of the 6 patients who are alive show bundle-branch block, 1 complete *A-V* dissociation and the other 3 have had a coronary occlusion and are more or less incapacitated. Only 2 of this group have lived more than 3 years after the *M* or *W* wave was first observed and both of these are incapacitated because of pain on effort.

4. Of 25 isolated cases observed during the past 2 years, 20 (80%) were from patients with coronary occlusion. Nine of the patients are dead; 13 of the remainder are from the groups suspected of having had a coronary occlusion, 1 suffered from hypertension and the 2 remaining cases are obscure and in 1 of these no other evidence of cardiovascular disease was found.

5. In most cases the *M* or *W* wave is probably due to an intra-ventricular conduction abnormality as a result of myocardial disease. Pathologic changes were widespread in the 3 cases in which necropsy was obtained. It is possible, however, that a congenital anomaly of conduction may occasionally produce complexes of this type.

6. In some cases the *M* or *W* complex has been present throughout the entire period of observation. In others, it has been relatively transient. Its appearance time following coronary occlusion is variable, the range observed in serial electrocardiograms being 1 day to 3 months.

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BOOK REVIEWS AND NOTICES.

1. A TEXTBOOK OF HISTOLOGY. Functional Significance of Cells and Intercellular Substances. By E. V. COWDRY, Professor of Cytology in the School of Medicine, Washington University, St. Louis. Pp. 503; 242 illustrations. Philadelphia: Lea & Febiger, 1934. Price, \$5.50.
2. ESSENTIALS OF HISTOLOGY. By SIR E. SHARPEY-SCHÄFER, F.R.S., Formerly Professor of Physiology in the University of Edinburgh. Thirteenth edition edited by H. M. CARLETON, M.A., B.Sc., D. PHIL., Lecturer on Histology in the University of Oxford, Research Fellow of New College, Oxford. Pp. 618; 721 illustrations. Philadelphia: Lea & Febiger, 1934. Price, \$5.00.
3. A TEXTBOOK OF HISTOLOGY. By ALEXANDER A. MAXIMOW, Late Professor of Anatomy, University of Chicago, and WILLIAM BLOOM, Associate Professor of Anatomy, University of Chicago. Pp. 662; 530 illustrations, some in colors. Second edition, completely revised. Philadelphia: W. B. Saunders Company, 1934. Price, \$7.00.

AMONG the new textbooks and new editions that annually herald the advent of the medical school year, those on histology are especially prominent this year. Sharpey-Schäfer's "Essentials," which in a half century has reached the enviable distinction of 13 editions and Maximow's fine volume, reflecting ably the brilliant studies of that lamented investigator, are now joined by Cowdry's text, written with all the charm and freshness of viewpoint of that well known prolific pen.

It would seem profitable to consider the 3 volumes together. Immediately one notices the effect of the world's economic situation. The Maximow has been reduced by 170 pages at a saving to the buyer of \$2.00. The English book (though costlier and larger than earlier editions) sells for less than the others, at a very modest price as medical textbooks go; while Dr. Cowdry's recognition of the pedagogic need for rigid selection has also permitted the attainment of a low price. This gives a cost for the 3 books of, 1.06, 0.81 and 1.10 cents per page respectively; and, while the Essentials' page is smaller in size, this is balanced by the use of smaller, though legible, type. One would indeed be embarrassed as to which to select for the average student. All are excellent books, clearly written, by masters in their own particular field, all are well illustrated and printed and all have recognized the need for stressing the relation of form to function. Each—as is inevitable, nay, even desirable—is especially strong in fields in which the author has chiefly labored. Thus Maximow's sections on the blood forming and destroying tissues are noteworthy, whether or not one agrees with his decided and rather extreme views on the subject. The Cowdry volume is especially strong on "The Blood, the Principal Integrator" and on the endocrine organs—these two sections together comprising a full quarter of the text. A surprising exception, is the relatively short space devoted in the Essentials to the endocrine organs; here, however, the lessons on nervous tissues and the central nervous system are unusually detailed, comprising more than one-fifth of the total space. It would seem, then, that the deciding factor for a prospective purchaser might well depend on the field in which his own chief interest lay. The illustrations are most numerous in the Essentials—least so in "Cowdry;" the former, however, are in the more diagrammatic style in vogue in English textbooks, while the quality of the latter is unusually high, both in subject and in execution. Cowdry has

sensibly omitted the simpler, hackneyed pictures that the student can easily comprehend from his own slides. The Maximow illustrations, less reduced in number from the first edition than the text, are good and more than twice as numerous as the Cowdry. Too many, however, especially in the Special Sense sections, are "redrawn from" or "after" other writers. "Cowdry" has a useful 21-page combined bibliography and author index; "Maximow" has wisely included appropriate references at the end of each chapter. None of these books meets the need for a reasonably complete presentation of human histology—and none of them is intended to do so. All 3 accomplish ably the purpose for which they were written.

E. K.

A TEXTBOOK OF PATHOLOGY. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S.C., Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg. Pp. 1047; 416 illustrations and 8 colored plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$10.00.

WHEN many medical publications are keeping in step with the times by retrenchments in size, it is a pleasure to find a new edition required in the short space of 2 years, and to see it augmented by 100 pages and more than 100 engravings. It is also a pleasure to see that morbid anatomy, a subject dead only "in the hands of those whose dull minds would take the breath of life from the most vital subject," requires expanded treatment after such a short period. In addition to really extensive revision, the following topics have been added: bacterial infections, immunity and allergy, trauma, von Gierke's glycogen storage disease, lead poisoning, localization of infection, rhinosporidiosis, Oroya fever, causation of anginal pain, tobacco hypersensitiveness, medionecrosis of the aorta, pneumonia in the newborn, duodenitis, stasis gall-bladder, chronic Bright's disease, renal infantilism, arrhenoblastoma, sweat gland carcinoma of the breast, lateral aberrant thyroid tumors, pituitary basophilic invasion, monocytic leukemia, the St. Louis type of encephalitis, bone tumors, together with new chapters on heredity and constitution and on diseases of the teeth. In a field already fortunate in its textbooks for students, this book has now firmly established itself as a leader.

E. K.

ELEKTROKINETIC PHENOMENA AND THEIR APPLICATION TO BIOLOGY AND MEDICINE. By HAROLD A. ABRAMSON, M.D. Pp. 331; 106 illustrations. New York: The Chemical Catalog Company, Inc., 1934. Price, \$7.50.

THOROUGHLY qualified both as experimenter and student of the literature, the author has presented the subject of electrokinetic phenomena in concise and readable form. It was observed by Reuss, in 1808, "that a direct electric current could forcibly transport the charged water molecules through a porous quartz or clay diaphragm." This phenomenon is known as electro-osmosis. The converse phenomenon, electrophoresis or cataphoresis, the electric transport of particles suspended in liquid, was observed but not understood by Reuss. From this beginning the author traces the development of the subject up to the present day. Of particular interest are the applications of electrophoresis to modern immunology. Measurement of the change in velocity in an electric field, of bacteria and other cells, brought about by antibodies, has thrown much light on the nature of these substances. To what extent electric charge of bacteria varies with virulence appears a promising field for further investigation. The reader is aided by an appendix in which the mathematical symbols are collected and defined.

M. McM.

LEHRBUCH DER INNEREN MEDIZIN, VOLUMES 1 AND 2. By DR. G. VON BERGMANN, with DRs. F. STROEBE (BERLIN), A. DOERR (BASEL), H. EPPINGER (VIENNA), FR. HILLER (MÜNCHEN), G. KATSCH (GREIFSWALD), L. LICHTWITZ (with A. RENNER) (NEW YORK), P. MORAWITZ (LEIPZIG), A. SCHITTENHELM (with E. HAYER) (KIEL), R. SIEBECK (HEIDELBERG), R. STAEHELIN (BASEL), W. STEPP (BRESLAU), H. STRAUB (GOETTINGEN), S. J. THANNHAUSER (FREIBURG I. BR.). Pp. 1708; 290 illustrations. Berlin: Julius Springer, 1934. Price, Rm. 45.

SIXTEEN authors under the capable leadership of Professor von Bergmann have produced what is probably the best German textbook on medicine. A two-volume work makes possible a more satisfactory presentation of the subject matter usually covered in the one volume to which all recent American texts on medicine are restricted. It permits, too, the inclusion of material not generally found in our textbooks. Worthy of mention in this regard is the introductory chapter (50 pages) dealing with such topics as the scope of internal medicine; the patient and his environment; the concept of constitution; the principles of heredity; also the chapters on the general principles of infection and immunity and of the treatment of infections (112 pages). Emphasis and clarity are enhanced by the judicious use of several kinds of type: bold face, capitals, italics, with small type in addition effecting the saving of valuable space. The illustrations, notably the many roentgenograms, are well done. The net result is a work that gives the student a broader, more philosophic viewpoint than a one-volume text can do, and at the same time does not swamp him in the mass of detail of a larger "system" of medicine.

R. K.

BRIGHT'S DISEASE. A Clinical Handbook for Practitioners and Senior Students. By J. NORMAN CRUICKSHANK, M.C., M.D., D.Sc., F.R.F.P.S. (GLAS.), M.R.C.P. (LOND.), Senior Assistant to the Muirhead Professor of Medicine, University of Glasgow; Assistant Physician, Glasgow Royal Infirmary; Visiting Physician, Southern General Hospital, Glasgow. Pp. 208. Baltimore: William Wood & Co., 1933. Price, \$3.75.

"THIS book has been written with the object of providing the practitioner and the senior student with a short account of the clinical application of modern views of the nature of Bright's disease." The bewildering mass of literature that has accumulated in recent years with their advances in knowledge of renal function and disease has created a real need for a digest of this material for the practitioner and student, a need which this excellent little volume is eminently qualified to fill. Chapters on the functions on the kidney, types of Bright's disease, etiology, treatment, tests of renal function, edema in Bright's disease, uremia, kidney structure, and technical details of some methods employed in estimating renal functional efficiency present these topics in a concise, adequate and lucid manner. The book is warmly recommended.

R. K.

DIE OPHTHALMOLOGIE DES SUSRUTA, ETC. Heft 22 of Studien zur Geschichte der Medizin. By DR. MED. ET PHIL. A. ALBERT M. ESSER, Augenarzt in Düsseldorf. Pp. 83. Leipzig: Johann Ambrosius Barth, 1934. Price, Rm. 7.50.

It is rather widely recognized that the history of ancient Hindu medicine is at the moment in a far from satisfactory condition. The labors of such philological historians as Reinhold Müller and the author, each working, to be sure, from different points of view, will doubtless clarify the situation ere long. On account of the long and devious course of Indian medicine,

Esser has chosen to study through various periods a cross section of the subject as treated by various writers—such as ophthalmology in this case—rather than treat of the individual or his period as a whole. This work on Susruta's Uttaratanttra follows similar studies by the author on the Bhavaprakasa of Bhavamisra. The translation occupies the bulk of the monograph.

E. K.

DIE DIÄTETISCHE BEHANDLUNG DER ALLERGIE BEI INNEREN ERKRANKUNGEN. By CARL FUNCK, M.D., Chief of the Section for Allergy and Disorders of Nutrition, Elizabeth Krankenhaus, Köln-Hohenlind. Pp. 92. Leipzig: Johann Ambrosius Barth, 1934. Price, Rm. 2.40.

BASED on the theory (unproved) that food allergy is based on an abnormal permeability of the gastro-intestinal mucosa for unsplit protein and the subsequent failure of the hepatic barrier, with the further etiologic factor of a "can-opener, cork-screw" diet, the author propounds his therapeutic doctrine. While the book contains many things of practical value and interest, there is unfortunately much that is open to question, and vehemence of statement often takes the place of logic. The differences of German diet from ours (magnified by a "Buy-German" propaganda) greatly lessen the value of the book for American readers.

R. K.

BONE GROWTH IN HEALTH AND DISEASE. By H. A. HARRIS, D.Sc. (LOND.), M.B., B.S. (LOND.), B.Sc. (WALES), M.R.C.S., M.R.C.P., Professor of Clinical Anatomy, University College and University College Hospital, London; Hunterian Professor and Arris and Gale Lecturer of the Royal College of Surgeons, etc. Pp. 248; 201 illustrations. New York: Oxford University Press, 1933. Price, \$10.50.

DIVIDED into three parts this monograph covers: I. Arrest of bone growth in systemic disease; II. Correlation of radiological appearance and histological structure of bone; III. Recent investigations in bone growth.

The treatise is interestingly written and well illustrated. The investigative data are not always convincing nor are the conclusions at all times well founded.

G. W.

THE CHEMISTRY OF THE HORMONES. By BENJAMIN HARROW, Ph.D., Associate Professor of Chemistry, College of the City of New York, and CARL P. SHERWIN, D.Sc., M.D., Dr.P.H., on the Staff of St. Vincent's Hospital and French Hospital, New York City. Pp. 227. Baltimore: The Williams & Wilkins Company, 1934. Price, \$2.50.

So much work has been done recently upon various hormones that even research workers in this field find it difficult to keep up with more than their own specialized interests. One need only mention the constantly growing list of pituitary hormones and their relationship to the gonads, thyroid and adrenals to realize that new information has been gathered so fast that confusion was unavoidable. A short monograph which sums up the isolation, chemistry and assay of the recognized hormones is, therefore, both timely and valuable.

The work is divided into nine chapters which cover the hormones of the thyroid, parathyroid, pancreas, pituitary, adrenal, testis, ovary, duodenal mucosa and plant tissues. The authors are to be congratulated upon a judicious choice of material, resulting in lucidity which would otherwise be impossible to attain. The bibliographies at the end of each chapter are more than adequate.

Although no more is claimed for the monograph than "a *practical* book—a book of use to the laboratory worker who wishes to prepare active hormone fractions, or to isolate a chemically pure hormone," the Reviewer feels that also the clinician, mainly interested in hormones from the standpoint of therapy or diagnosis, may derive a clearer view of these substances from a knowledge of their preparation and chemistry. D. D.

BRUCELLA INFECTIONS IN ANIMALS AND MAN. By I. FOREST HUDDLESON, Department of Bacteriology and Hygiene, Michigan State College. Introduction by WARD GILTNER, Dean, Division of Veterinary Medicine, Michigan State College. Pp. 108; 24 illustrations, 2 in colors. New York: The Commonwealth Fund, 1934. (No price given.)

THE growing recognition of the importance of Brucellosis (infectious abortion, undulant fever) in human and veterinary medicine makes this monograph especially timely. The topics covered are: a brief history of the three species of *Brucella*; descriptions of morphology, staining and cultural characteristics; methods of isolating the organisms; the pathology of *Brucella* infections; diagnostic methods (agglutination, skin tests and opsonic activity); and methods of differentiating the species of *Brucella*. There is a bibliography of 188 titles and an index. The book is well written, statements are brief, directions clear and illustrations well chosen.

H. R.

SÉCRÉTION INTERNE ET RÉGÉNÉRESCENCE. By N. E. ISCHLONDSKY, M.D. Pp. 336; 72 illustrations. Paris: G. Doin et Cie, 1933. Price, 90 fr.

INSERTED just before the preface are over three pages of corrections of typographic errors. Thirty pages would not suffice to list the multitude of fallacies and absurdities of the text.

R. K.

THE MANAGEMENT OF FRACTURES, DISLOCATIONS AND SPRAINS. By JOHN ALBERT KEY, B.S., M.D., Clinical Professor of Orthopedic Surgery, Washington University School of Medicine; Associate Surgeon, Barnes, Children's, and Jewish Hospitals, St. Louis, and H. EARLE CONWELL, M.D., F.A.C.S., Orthopedic Surgeon for the Tennessee Coal, Iron and Railroad Company, Birmingham, Alabama, etc. Pp. 1164; 1165 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, \$15.00.

PROBABLY no recent book covers the field of *fractures and joint traumata* so thoroughly. The book is of particular value in that it is composed entirely of the personal experience of two surgeons who have had the opportunity to handle an enormous number of cases. The details of treatment are personal and not encyclopedic; the illustrations are good and the general composition of the book satisfactory.

G. W.

PATHOLOGIE DER MITOSE. By GEORG POLITZER, Privatdozent der Embryologie an der Wiener Universität. Band 7 of Protoplasma-Monographien. Pp. 238; 113 illustrations. Berlin: Gebrüder Borntraeger, 1934. Price, Rm. 16.20.

THIS useful booklet adequately brings together in a small but important field information not otherwise readily available. Under the headings: Morphology (pyknosis, rhexis, polarization and cytoplasmic changes), Changes

in Rhythm of Division, Cell Division in Carcinoma and in Hybrids, Actinic and Chemical Effects, The Problem of Specificity, the various abnormalities of cell division are systematically presented by one whose individual contributions to the subject has been not inconsiderable. A fifteen-page reference list facilitates more extensive study. The sections must be read in detail to be comprehended, both on account of the nature of their contents and as no summary is presented of the many observations or the conclusions to be drawn from them.

E. K.

THE TEACHING OF PREVENTIVE MEDICINE IN EUROPE. (University of London Heath Clark Lectures, 1932, delivered at The London School of Hygiene and Tropical Medicine.) By CARL PRAUSNITZ, M.D. (BRESLAU), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Professor of Hygiene in the University of Breslau. Pp. 180; 37 illustrations. New York: Oxford University Press, 1933. (Price not given.)

This little volume contains the Heath Clark Lectures delivered at The London School of Hygiene and Tropical Medicine by one of the foremost authorities on Preventive Medicine. The contents divide themselves into two parts: the history, philosophy and outlook of the whole preventive medicine movement, and a well chosen summary of the activities in the fields of practical hygiene and preventive medicine teaching in the several European countries.

Although the introduction mainly concerns itself with the first of these objectives, the other chapters setting forth the detailed program in each country are also flavored with the mature philosophy and conservative criticism of this distinguished author.

Professor Prausnitz rightly points out that there should be two types of training available for the future of Preventive Medicine: the training of the specialist who would pursue a career concerned with the practical applications of the State's share in the hygiene program, but even more important the imbuing of every prospective physician with the broad principles of modern Preventive Medicine so that he may apply these principles to every case in his future practice. The volume is recommended for those who desire another authoritative discussion of the methods used in European countries to insure health and sanitation and to teach the newer philosophy of Preventive Medicine.

E. T., JR.

CRANIOCEREBRALE SCHEMATA FÜR DIE RÖNTGENOGRAPHISCHE LOKALISATION. By PROF. DR. A. SCHÜLLER, Consiliarius am Zentral-Röntgen-Institut des allg. Krankenhauses in Wien, und DR. H. URBAN, Assistent der Psychiatrisch-neurologischen Universitäts-Klinik in Wien. Pp. 8; 17 figures and 1 celluloid stencil. Leipzig: Franz Deuticke, 1934. Price, M. 4.

In this pamphlet the authors describe a method for the roentgenographic localization of intracranial lesions and the determination of the relationship of pathologic processes of the calvarium to the surface of the underlying brain. The method is briefly and clearly described. The necessary cross-section and surface drawings of the brain and skull and a celluloid stencil required to employ this method of localization are supplied with the description. The method is exceedingly simple and would appear to be, as stated by the authors, sufficiently accurate for all practical purposes. The procedure is one that can be readily employed in any Roentgen laboratory, as the technique, with slight modifications, utilizes the usual views employed in head radiography. The method is recommended to those interested in the localization of lesions capable of demonstration by the Roentgen ray.

K. K.

EPIDEMIC MYALGIA. BORNHOLM DISEASE. By EJNAR SYLVEST, M.D. With a Foreword by DR. TH. MADSEN, Director of the Danish State Serum Institut, Copenhagen. Translated from the Danish by HANS ANDERSON, M.D. Pp. 155. Copenhagen: Levin & Munksgaard, 1934. Price, D. Cr. 8.

ABOUT 10 years ago our Atlantic Seaboard was visited by what appeared to be a new disease with such strikingly painful symptoms that it attained prominence in the newspapers as "devil's grip;" in medical journals as epidemic pleurodynia. This monograph treats of the same disease under the name of epidemic myalgia, and traces its course through Scandinavia, England, Germany and North America, since its first recognized appearance in Iceland in 1856. A disease that has numbered over 10,000 victims in Denmark alone in recent times, even though not threatening to life, is well worth the attention here given to it.

E. K.

THE LIFE OF SIR ROBERT JONES. A Biography of the World's Greatest Orthopedic Surgeon, the Friend of Crippled Soldiers and Children. By FREDERICK WATSON. Pp. 327; illustrated. Baltimore: William Wood & Co., 1934. Price, \$3.75.

AFTER reading this glowing biography, it is hard to decide whether Robert Jones was greater as a scientist or as a man. Richly endowed intellectually and with the good fortune to come early under the influence of the great H. O. Thomas, Jones' genius was well prepared to utilize the unequalled opportunities of the war to advance knowledge of orthopedics to a position far beyond its previous status. Americans have good reason to be grateful for the invaluable training that he gave their orthopedists at this critical time. A highminded, optimistic humanitarian, "only easy-going so long as his principles were unchallenged," righteously indignant on occasion, but by nature patient and humorous, these are the qualities that will be recalled by his friends and patients. The story of this great life is divided into a Prelude (1857-1891); Consolidation (1891-1914); the Disabled Soldier (1914-1920); Harvest (1920-1933). The inspiration that it carries for the young medical man is hard to overestimate.

E. K.

APPLIED PHYSIOLOGY. By SAMSON WRIGHT, M.D., F.R.C.P., John Astor Professor of Physiology, University of London. Pp. 604; 195 illustrations, 1 colored plate. Fifth edition. New York: Oxford University Press, 1934. Price not given.

THIS edition maintains the former purposes of this book of describing physiology from the laboratory and scientific standpoint and of adding to each subject the applications of the facts and principles to clinical medicine, explaining the signs and symptoms as far as possible. The author has made material changes to no less than forty subjects and has added a great many illustrations. The book is to be recommended for students but will be perhaps most helpful to the clinician to explain the physiologic reasons for the symptoms and signs of a particular case. The teacher of clinical medicine might well peruse the appropriate pages before giving his lecture. No subject that is truly important in human medicine has been overlooked. The physiology of the nervous system is perhaps treated with unnecessary length but, at all events, the author shows the relationship between the functions and anatomy of different parts as correlated and harmonized through the nervous connections. The author continues to use the glossary of international anatomic nomenclature, the so-called B.N.A., so that terms unusual to the readers in the United States may be easily found. Indeed, some places in the text he uses both terminologies. This new edition is a welcome one on the shelf of the practical and laboratory medical man.

H. F.

THE CYCLOPEDIA OF MEDICINE. GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief, and EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associate Editors: W. WAYNE BABCOCK, A.M., M.D., CONRAD BERENS, M.D., P. BROOKE BLAND, M.D., FRANCIS L. LEDERER, B.S., M.D., and A. GRAEME MITCHELL, M.D. (CHARLES E. DEM. SAJOUS, M.D., LL.D., Sc.D., Founder and First Editor). Twelve Volumes and Desk Index Volume; each illustrated with half-tone and line engravings, also full page color plates. Philadelphia: F. A. Davis Company, 1931-1934. Price, \$120.00.

To review a medical book is ordinarily not so difficult a task: a careful reading and then the expression of an opinion by one qualified to do so in that field. To review a cyclopedia, however, is quite a different matter. To read word for word the twelve volumes is out of the question, let alone to presume to pass judgment on all the contents. The Reviewer therefore did two things: leaf through the volumes, page for page, reading such articles as caught his fancy; and, what is more to the point, use the books for some months as a reference work, which after all is their purpose. He was pleased with what he found: most topics were covered adequately, some exceedingly well, and only very few were disappointing. Perhaps he would have been even more pleased had he had the index volume to guide him: this has not yet appeared. Upon it will depend in no small measure the usefulness of the work, for while there is an alphabetic arrangement of indexing subject matter, there has not always been followed a set scheme of indexing (so one finds, *Caffeine*: see *Coffee*; *Calabar Bean*: see *Physostigma*; *Nephritis*: see *Kidneys*; *Blood*: see *Hematology*). The Editor has succeeded remarkably well in the difficult task of avoiding duplication and of preserving proper balance in space used by the 700 contributors. One might object, however, to the allotment of 80 pages to vascular tumors and only 23 to typhoid fever; or of 5 columns to apocynum, only 1 to allonal, and why any space at all to *Adonis vernalis*, or 3 columns to *scoparius* of which "there is now no official preparation." Hay fever has been covered twice, and physical allergy by the same author, but food allergy as a factor in headache or gastro-intestinal disorders is not mentioned. Of particular excellence are the sections on the cardiovascular system, and the gastro-intestinal tract. Weakest are pharmacology and endocrinology. The illustrations are numerous and well done. R. K.

THE PHYSIOLOGICAL EFFECTS OF RADIANT ENERGY. American Chemical Society Monograph No. 62. By HENRY LAURENS, Ph.D., Professor of Physiology, Tulane University School of Medicine. Pp. 610; 104 illustrations. New York: The Chemical Catalog Company, Inc., 1933. Price, \$6.00.

EXHAUSTIVE as is this substantial volume, it fails to live up to its still more exhaustive title. The discussion is limited to certain physiological effects of the wavelengths present in the solar spectrum. The effects of other radiant energy—for example, of Roentgen rays and rays from radioactive substances—are not described. Moreover, certain physiological effects of the solar spectrum, such as vision and plant photosynthesis, are scarcely mentioned. These omissions are of course quite proper, since the topics mentioned have been exhaustively dealt with in other books; but the title might have been more indicative of the content. The author has dealt in an adequate and scholarly fashion with the components of the solar spectrum chiefly in their relations to mammalian metabolism, to phototherapy, and to the production of pathological effects. Five chapters (224 pages) are devoted to effects upon metabolism, including the relationships between radiation and vitamins. Two chapters (39 pages) summarize the effects upon wounds and certain diseases, while five others deal respec-

tively with effects on the skin, the eye, the circulatory system, the blood, and body temperature, respiration and blood reaction. Photodynamic sensitization is discussed at some length and the effects upon microorganisms, toxins, proteins, enzymes, etc., are dealt with in an adequate fashion. The chapter on the physics of radiant energy includes brief descriptions of methods of measurement and an extended account of the spectral distribution of the energy from various artificial sources and of the solar radiation incident at various places and under various conditions. The mechanism of physiological action of the radiant energy is covered in nine pages, which fact strikingly emphasizes the present paucity of our knowledge of this essential subject. The primary aim of the author has been, not to write a critical review, but to compile a source book. In this rôle his volume should prove very useful. R. Z.

NEW BOOKS.

- Physiology in Health and Disease.* By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Pp. 1156; 182 illustrations. Philadelphia: Lea & Febiger, 1934. Price, \$9.00.
- Benjamin Rush.* Physician and Citizen (1746-1813). By NATHAN G. GOODMAN. Pp. 421; illustrated. Philadelphia: University of Pennsylvania Press, 1934. Price, \$4.00.
- The Radiology of Bones and Joints.* By JAMES F. BRAILSFORD, M.D. (B'HAM.), M.R.C.S. (ENG.), Radiological Demonstrator in Living Anatomy, the University of Birmingham, etc. Pp. 500; 310 illustrations. Baltimore: William Wood & Co., 1934. Price, \$9.00.
- Franklin Paine Mall. Anatomist.* By FLORENCE RENA SABIN. Pp. 342; 6 illustrations. Baltimore: The Johns Hopkins Press, 1934. Price, \$2.75.
- Lincoln's New Salem.* By BENJAMIN P. THOMAS. Pp. 128, illustrated. Springfield, Ill.: The Abraham Lincoln Association, 1934. Price, \$1.00.
- Sex-Hygiene.* What to Teach and How to Teach it. By ALFRED WORCESTER, A.M., M.D., Sc.D., HENRY K. OLIVER, Professor of Hygiene, Harvard University. Pp. 134. Springfield, Ill.: Charles C Thomas, 1934. Price, \$2.50.
- Conception Period of Women.* By DR. KYUSAKU OGINO, Head of the Gynecological Section of Takeyama Hospital, Niigata, Japan (Nippon). English Translation by DR. YONEZ MIYAGAWA, Director of Government Institute for Infectious Diseases, Tokyo Imperial University, Hongooku, Tokyo, Japan. Pp. 94; 22 tables. Harrisburg: Medical Arts Publishing Company, 1934. Price, \$1.00.
- Cataract.* Its Etiology and Treatment. By CLYDE A. CLAPP, M.D., F.A.C.S., Associate Professor of Ophthalmology, Johns Hopkins University; Professor of Ophthalmology, University of Maryland, etc. Pp. 254; 92 illustrations. Philadelphia: Lea & Febiger, 1934. Price, \$4.00.
- Synopsis of Genitourinary Diseases.* By AUSTIN I. DODSON, M.D., F.A.C.S., Richmond, Virginia. Pp. 275; 111 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, \$3.00.
- Studies in Blood Formation.* By T. D. POWER, M.D., M.R.C.P., D.P.H., D.P.M., Deputy Medical Superintendent, Brentwood Mental Hospital. Pp. 124; 25 illustrations. London: J. and A. Churchill, Ltd., 1934. Price, 8s. 6d.
- The Doctor in History.* By HOWARD W. HAGGARD, Associate Professor of Applied Physiology in Yale University. Pp. 408; illustrated. New Haven: Yale University Press, 1934. Price, \$3.75.

Krebs im Lichte biologischer und vergleichend anatomischer Forschung. By MED. DR. JOSEF L. HARTSCHNEIDER, Lintz a. d. Donau. Volume 2, No. 1. Albuminoide, Schilddrüse, Kropf, Hypophyse, Eierstock, Adenosis. Pp. 94; 19 illustrations. Leipzig: Franz Deuticke, 1934. Price, Rm. 5, S. 7.50.

The Patient and the Weather. Vol. 3 Mental and Nervous Diseases. By WILLIAM F. PETERSEN, M.D., with the assistance of MARGARET E. MILLIKEN, S.M. Pp. 375, lithoprinted; 192 illustrations. Ann Arbor: Edward Brothers, Inc., 1934. Price, \$5.00.

The Cyclopedia of Medicine, Volumes 11 and 12. GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief, and EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associate Editors: W. WAYNE BABCOCK, A.M., M.D., CONRAD BERENS, M.D., P. BROOKE BLAND, M.D., FRANCIS L. LEDERER, B.S., M.D., A. GRAEME MITCHELL, M.D. Pp. Vol. 11, 1111; Vol. 12, 1004. Illustrated with half-tone and line engravings, also full page color plates. Philadelphia: F. A. Davis Company, 1934. Price, \$120.00 set. (Review, p. 862.)

NEW EDITIONS.

Rules for Recovery from Pulmonary Tuberculosis. A Layman's Handbook of Treatment. By LAWRASON BROWN, M.D., Saranac Lake, N. Y. Pp. 275. Sixth edition thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$1.75.

Applied Anatomy. By GWILYM G. DAVIS, M.D., Late Professor of Orthopedic Surgery and Associate Professor of Applied Anatomy in the University of Pennsylvania. Pp. 717; 674 illustrations, many in colors by ERWIN F. FABER. Ninth Edition, reset, reillustrated and completely revised by GEORGE P. MULLER, M.D. Assisted by DRs. B. J. ALPERS, R. A. KIMBROUGH, JR., S. W. MOORHEAD, I. S. RAYDIN and S. D. WEEDE. Philadelphia: J. B. Lippincott Company, 1934. Price, \$9.00.

Practical Obstetrics. By P. BROOKE BLAND, M.D., Professor of Obstetrics, and THADDEUS L. MONTGOMERY, M.D., Associate in Obstetrics, Jefferson Medical College, Philadelphia. Pp. 730; 516 illustrations, including 21 colored plates. Second edition. Philadelphia: F. A. Davis Company, 1934. Price, \$8.00.

The evident need for a medium size volume on obstetrics is manifested in the early appearance of a second edition of this excellent textbook. The teaching is modern but conservative, and stress is laid upon the practical aspects of the subject, especially as regards hygiene and home obstetrics.

A Manual of the Practice of Medicine. By A. A. STEVENS, A.M., M.D., Honorary Consulting Physician to the Philadelphia General Hospital; Consulting Physician to St. Agnes Hospital, Philadelphia. Pp. 685; 15 figures. Thirteenth edition, revised. Philadelphia: W. B. Saunders Company, 1934. Price, \$3.50.

That it has reached its thirteenth edition is the best evidence of the popularity of this excellent little manual.

Allergy and Applied Immunology. By WARREN T. VAUGHAN, M.D., Richmond, Va. Pp. 420; 23 illustrations, 36 tables and 18 charts. Second edition. St. Louis: The C. V. Mosby Company, 1934. Price, \$5.00.

An excellent book for general practitioners, students, and patients. There has been added a very useful appendix with diet lists, recipes, food diaries, and the like.

Diabetic Manual for Patients. By HENRY J. JOHN, M.A., M.D., F.A.C.P., MAJ. M.R.C., Director of the Diabetic Department and Laboratories of The Cleveland Clinic. Pp. 232; 47 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1934. Price, \$2.00.

PROGRESS OF MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY IN THE UNIVERSITY OF COLORADO,

AND

GEORGE JOHNSON, M.D.,

PROFESSOR OF NEUROPSYCHIATRY, LELAND STANFORD UNIVERSITY.

TRAUMA OF THE CENTRAL NERVOUS SYSTEM.

THE increasing frequency of injuries to the central nervous system associated as it is with the high speed of modern life has presented a most important problem in the practice of medicine. The mechanization of our daily life, both in transportation and in industry, has been attended by increasing hazards which have taken an unusual toll in injuries to the brain and spinal cord. That there should still be considerable difference of opinion in regard to the various features of this problem is not remarkable when we consider that the tremendous increase in the incidence of brain injuries has been paralleled by an equally tremendous change in the concepts of neuropathology, neurophysiology, neurosurgery, and psychobiology. This review will consider these various concepts.

Pathology.—Winkelman and Eckel¹ review the extensive literature in this field, especially during the early stages, and present the results of their own investigations. They report that the brain of the patient who dies hours after a severe head trauma often shows a subarachnoid hemorrhage with maceration of the brain on the under surface of the frontal and temporal lobes. They believe this to be due to the lack of an adequate water bed between these parts of the brain and the base of the skull. Gross hemorrhage in the brain substance is fairly common with contusion or maceration of the tissue in the immediate neighborhood. The hemorrhage, far more frequently than is thought, is due to *contre-coup*. Subdural bleeding is a less frequent finding and epidural hemorrhage comparatively rare. On section, aside from gross hemorrhages, contusion and maceration, intense congestion, edema and petechiæ are frequently encountered. The latter are frequently limited to the subcortical white matter as in various infections, intoxications and blood dyscrasias. The onset of edema increases the damage to the brain. In accord with Apfelbach, they do not find edema present

within the first several hours or after the third day. When edema does occur, there is interference with the blood supply to the brain with subsequent ischemic changes in the ganglion cells and areas of focal necrosis similar in every way to the areas resulting from obstruction to the minute bloodvessels from any cause (arteriosclerosis, severe infections and intoxications). The development of pial-cortical adhesions could be traced from the beginning as the result of subarachnoid hemorrhages and secondary reaction. There appeared to be convincing evidence in the brains of patients with severe head trauma, especially those in whom unconsciousness had been prolonged, that most of those patients have organic changes in the brain which explain the post-traumatic symptom complex usually characterized as "traumatic neurosis."

Rand and Courville,² have investigated the cellular reactions following injury. The microglia exhibit changes depending on the severity and age of the injury. Occurring soon after injury they show as vacuolization, mitotic and amitotic cell division, swelling of the major processes and transitional changes, including the formation of fat granule bodies. The authors agreed with the experimental observers³ that the microglia exercise a phagocytic rôle, the activity of which is mainly focal, confined to the place of lesion. In contrast, the rôle of the oligodendroglia is usually general. The early changes are the acute, more or less uniform swelling in all portions of the brain and may occur promptly, observed for instance in a person killed outright. Of the classic neuroglia, they found that in the first few days following trauma, the astrocytes in the immediately adjacent area undergo regressive changes with the formation of ameboid-glia. In the zone nearest the point of injury, the cells undergo complete destruction. Beyond this zone, active proliferation takes place. Gliosis occurs only as a result of tissue destruction, consequently remains a purely local affair. From their studies, they express the belief that the remote clinical sequelæ of injuries are largely to be interpreted on the basis of focal and distant cortical injuries and not from generalized gliosis.

In the production of the cerebral damage by *contre-coup* injury, interesting observations have been made by Le Count and Apfelbach⁴ and Vance.⁵ They demonstrated that *contre-coup* lesions occur only when the patient's head is injured while in motion. In such circumstances, the brain lags behind and is most closely applied to the after-coming portion of the skull. The skull is flattened at the point of impact and the brain immediately beneath is directly injured by this local application of force. In addition, however, because the axis of the skull is abruptly shortened at right angles to the plane of impact and because the brain is most closely applied to the bone directly opposite the point of impact, the most severe injury occurs at this place.

The management of patients suffering from the immediate effects of cerebral trauma is dependent upon two principal views of intracranial pressure relationships. In the opinion of Russel,⁶ "It is important to bear in mind that a degree of increase of intracranial pressure provides a powerful means of controlling hemorrhage from torn capillaries and veins. In this way cerebral edema may prevent hemorrhage and correspondingly, the artificial reduction of intracranial pressure may aggravate it." In Dandy's⁷ opinion, also, the immediate effect of trauma to the brain is the same as in any other soft tissue, mainly

swelling due to hemorrhage and edema. Nature's method of combating this increased volume in the closed cranial cavity is to withdraw fluid from the ventricular and subarachnoid systems and send it into the blood. The evidence of the state of balance existing between this increasing pressure and Nature's efforts to compensate for it, is to be found in the clinical observation on (1) the state of consciousness, (2) restlessness, (3) involuntary micturition or defecation, (4) rate and quality of the pulse and (5) respirations, and (6) the temperature. Of these the state of consciousness is the most important of all objective data. If a patient is unconscious, he has intracranial pressure beyond a certain degree of compensation which may be considered the margin of safety. Likewise, restlessness, a labile and increasing pulse; rapid, shallow and irregular respiration and a temperature above 101.5° or 102° F., are signs indicative of a failing compensation in intracranial pressure relationships. In accord with this view, Dandy states that "the only treatment up to a certain point in acute injuries is absolute rest." If after a period of 5 to 6 hours, consciousness improves or remains unchanged and the other signs remain within the limits of compensation, recovery will probably be spontaneous. If after this arbitrary period coma deepens and other signs indicate a break in compensation, recovery is practically impossible except for constant relief of pressure which can be obtained only by a subtemporal decompression.

An opposing viewpoint is presented by Munro,⁸ who cites the work of Cushing,⁹ Forbes¹⁰ and Forbes and Wolff.¹¹ They demonstrated that following a rise in intracranial pressure there is a slowing of the blood flow in and dilatation of the veins and arteries, the circulation being maintained (without increase in the systemic blood pressure) by a rise in pressure in the cerebral capillaries, arterioles and smaller arteries. Following a further rise in intracranial pressure, the cerebral circulation is then reestablished. This compensation may occur by steps. Such slowing of the capillary circulation is equivalent to anoxemia applied to the tissues of the brain generally. Depending upon the degree and the length of time it is present, there is a proportional cellular destruction, petechial softening, edema, further stasis and stagnation and capillary hemorrhage. Small areas of destruction may coalesce into larger areas with further spreading edema and further rise in intracranial pressure. These and further observations show, in Munro's opinion, "that cerebral venous and capillary pressures are approximately equal to intracranial (cerebrospinal fluid) pressure and they rise and fall with it. This high intracranial pressure cannot cause hemostasis without causing anoxemia and necrosis of the brain. By the same token lowering a high intracranial pressure by lumbar puncture decreases venous bleeding, because the venous pressure falls with the lowering of the cerebrospinal fluid pressure. The venous pressure is high because the intracranial pressure is high. Arterial pressure is rarely a factor since it is not affected until the intracranial and cerebral venous pressures approach arterial diastolic pressure, *i. e.*, 900 to 1100 mm. of water. Obviously arterial bleeding can never be checked by increased intracranial pressure; capillary stasis and death would take place long before such an intracranial pressure (1600 to 2000 mm. of water) could act on the arterial stream."

In keeping with these views, the treatment of acute injury rests upon measures designed to reduce the intracranial pressure by the artificial reduction of brain volume and the removal of excess fluid. The fundamental treatment of the patients reported by Munro consisted of a combination of therapeutic dehydration and decompression by lumbar drainage. For dehydration, 50% glucose intravenously, repeated once or twice if necessary, and a saturated solution of magnesium sulphate by rectum, repeated every 3 or 4 hours for 3 or 4 doses, were the measures used. Repeated lumbar drainage checked by manometric readings provides a means of removing excess fluid and of measuring the effectiveness of the other procedures in the control of intracranial pressure. Dehydration is properly limited to cases of edema or to use as a preliminary emergency treatment in cases of contusion and laceration. Lumbar puncture is suitable, however, for all three types of uncomplicated brain injuries. The edema is relieved because, with the reduction of intracranial pressure to normal, the venous congestion is corrected and the reactivated circulation allows the partially damaged asphyxiated cells to recover as much as possible. The excess intracellular and perivascular fluid is then absorbed and the brain volume is thus returned to normal. In contusions and lacerations, the excess unabsorbed fluid is mechanically removed together with a small amount of free blood and the meningocytes, if the drainage be repeated often enough, are aided in the uncorking of the absorptive channels in the arachnoidal villi. In those cases that are not immediately fatal, this treatment is expected to cause a progressive improvement in the patient's signs and symptoms. If this does not occur and toxic dehydration and meningitis can be ruled out, exploratory bilateral temporal trephine is considered indicated. This serves to eliminate the possibility of sub- or extradural hemorrhage or of one of the rarer forms of brain injury.

Although Russel⁶ contends that morphin is "useful and can apparently be given without danger," there is general agreement^{7, 8} that its use is hazardous as it masks symptoms and tends toward respiratory depression. Also, the meager information given by the Roentgen rays in regard to the true condition of the patient rarely warrants the disturbance of the patient's rest to make these examinations.

In considering the late effects of head trauma there have been several contributions during the past year. Straus and Savitsky¹² in an extensive review direct attention to the organicity of the so-called post-concussion syndrome. They deplore the attitude of hostility evidenced by the general medical profession toward the patient who exhibits personality changes after head trauma. They emphasize the necessity of preserving objectivity and the spirit of clinical investigation in the cases of patients who present symptoms which are confusing in the picture of common syndromes. They direct attention to a scheme of procedure which utilizes modern methods of investigation in establishing the nature of post-traumatic reactions. Of first importance is a careful exhaustive neurologic examination. Recently so much stress has been put on psychologic and social factors in the nervous symptoms that adequate neurologic examination has been neglected. Attention to detail with especially complete investigation for slight defects which may indicate focal lesions will result in fewer reports of "negative

neurologic findings." Psychologic and psychiatric surveys should likewise be more complete than simply limited interviews. Careful studies of the conscious processes (the nature of the intellectual processes, the quality of the sensory experience and the status of the volitional tendencies), should be made. The ready fatigability, emotional lability, difficulty in thinking and mild symptoms of mental defects are recognized as early symptoms in such organic psychoses as early dementia paralytica, cerebral arteriosclerosis and brain tumor but are frequently ignored or attributed to simulation when observed as part of the post-traumatic reaction. The use of the special techniques developed in the psychologic laboratories by which memory, fatigability, learning ability, etc., are investigated, have proved helpful both diagnostically and in suggesting at times practical methods of rehabilitation. The commonly used intelligence test, the Binet-Simon, and the performance test are of value only if there is the control of a comparable test before the trauma. Too much emphasis has, they believe, been placed in the past upon the necessity of establishing the presence of intellectual defects in cases of organic disease of the brain. The defect may be largely limited to the affective sphere. There may be no difficulty in solving simple arithmetical problems, but there may be impairment of judgment in the sense of inability to evaluate ethical and social problems, lack of earnest relation to reality, loss of interest and initiative and other defects in the volitional processes.

The extensive distribution of the visual pathways through the brain has lead these authors to attach especial importance to complete ophthalmologic surveys. Extensive defects in the fields may exist without any complaint. Consequently, complete studies of the visual fields including the color fields must be carried out. The usual approximate tests made in office practice are not sufficient but complete study using a correct technique, proper illumination, tangent screen, etc., must be made. Ring scotomas have been frequently described after head injury and the suggestion is made that these may be due to the fatigability which runs through the whole clinical picture of the postconcussion state.

The frequency of dizziness as a complaint indicates the need of a thorough study of the vestibular and auditory functions. Lithicun and Rand¹³ found abnormal responses to vestibular tests in all of 36 patients who complained of post-traumatic dizziness. Five of these patients were neurologically normal. By using the audiometer, Groves¹⁴ found some degree of deafness in 31 of 42 patients with head injuries. Twelve of the patients might easily have passed for persons with normal hearing. These patients showed so called patchy tone gaps.

The use of encephalography is advocated by Straus and Savitsky as well as by others¹⁵ as giving definite information of changes in the brain. Despite the absence of normal controls, the distortions of the ventricular system, basal cisterns and cortical markings are such that if adequate care has been taken to follow a uniform technique in the encephalographic procedure, much valuable information may be secured in regard to the site of lesions. Penfield directs attention to the therapeutic value of encephalography in post-traumatic headaches. His explanation is that the air serves to break up adhesions in the pia-arachnoid.

In evaluating the evidence of organic injury, Kennedy¹⁵ gives the following criteria:

A. *Absolute Criteria*: 1, Roentgen evidence—skull fracture; 2, bloody spinal fluid; 3, bleeding from the orifices, especially from the ears; 4, focal cerebral palsies.

B. *Presumptive Criteria in the Order of Their Importance*: 5, Convulsive states proved to be post-traumatic; 6, ventricular distortions proved to be post-traumatic; 7, history of prolonged unconsciousness; 8, history of adequate trauma with especial consideration of the occurrence of vomiting following the injury. These units are in a real sense measurable, he states, and are instruments for establishing the fact of brain injury. The first four units, together with Nos. 7 and 8, can be determined with accuracy. Convulsive states are often complained of but are not always readily seen. One may satisfy oneself of their reality by provoking an attack in many instances by cocaine or hyperventilation; this evidence is of value when positive. Headaches and dizziness are well nigh imponderable factors after head injury. However, if they persist for more than 4 months in a man under 60, ununited to any of the first seven premises of brain injury, they are to be regarded as suggested neuroses unfounded in structural change.

The symptomatology of head injuries has been studied more carefully from a neurologic than from a psychiatric point of view. Since the important paper by Meyer¹⁷ there have been few detailed psychiatric studies. Schilder¹⁸ examined 35 cases suffering from severe head injuries utilizing newer psychologic apparatus in an effort to correlate symptomatology and psychophysiologic mechanisms. He emphasizes the significance of extensive periventricular hemorrhage in the final elaboration of the disturbance in the memory, in the judgment and in the Korsakow's pictures. Straus and Savitsky¹⁹ distinguish three types of psychogenic disturbances following trauma, the Terror neuroses, Psychoneurosis precipitated by trauma, and Secondary psychologic elaborations. The terror neurosis is the direct reaction to the sudden threat to ego integrity, the psychosomatic response to the overwhelming of the individual by impending calamity. It is not often seen in head injuries for the automobile and industrial injuries happen so suddenly that there is little time for the patient to be impressed by the terrifying prospect of impending destructions. The psychoneurotic syndromes usually appear immediately after the injury and their further course hardly differs from that of the usual psychoneurotic except for the presence of the compensation problem. The secondary psychologic elaborations are frequent. They appear superimposed on organic sequelæ and usually disappear after satisfactory financial settlements even though the organic sequelæ persist.

Hall and Mackay²⁰ believe that the post-traumatic neuroses do not differ in any essential way from most other non-traumatic neuroses. The majority of these neuroses fall into one of three groups: Post-traumatic Neurasthenia, Post-traumatic Anxiety Neurosis and Post-traumatic Hysteria. They point out that there must be some pre-existing factor present to determine the development of the neurosis. The fact that great numbers of patients who have received the most severe injuries do not develop a neurosis, while in others the slightest injury suffices to precipitate a severe nervous state, suggests strongly

that people who develop post-traumatic neuroses already had the psychologic basis for the breakdown and that the injury served merely as a precipitant. Schaller and Somers²¹ found that after recovery from a post-traumatic neurosis had begun a certain point was reached when recovery ceased and the patient remained at a standstill or retrogressed. It thus appeared that after the immediate illness had been alleviated, the untoward circumstances in connection with the injury adjusted, the fight for compensation ended, the repeated medical examinations stopped and the patient back at work, there still persisted a personality defect which rendered the patient subnormal. Treatment of the post-traumatic features according to Hall and Mackey centers around the establishment of a proper rapport with the patient, the settlement of compensation claims promptly and by a lump sum and the prompt vocational reestablishment of the patient. Aside from these special features the treatment employs the same procedures indicated in the case of any psychoneurosis.

GEORGE JOHNSON.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 15, 1934.

A Reconstruction of the Basal Ganglia of the Adult Human Brain.—W. H. F. ADDISON and DORIS ACORN FRASER (Laboratory of Anatomy, University of Pennsylvania). To understand thoroughly the significance of the basal ganglia it is necessary to know both the morphology of the nuclei of which they are composed and the connections of the nuclei to other regions of the brain. The anatomic investigation of this large mass of the brain has been relatively slight while the great

bulk of the literature has been contributed principally in the fields of neuropathology and clinical medicine. Because of the importance of the extrapyramidal system clinically it has seemed desirable to make a reconstruction of the corpus striatum and related parts based on the adult human brain. Series of sections were made of the central core of the brain at $50\ \mu$ both in a sagittal plane and in a plane at right angles to the midbrain. Projection drawings were then made, at a magnification of 5, of every eighth section. Wax plates were cut out according to these drawings and stacked to give a reconstruction at an enlargement of 5 in each dimension.

The reconstruction shows very well the shape and size of the striatum, the red nucleus, the substantia nigra and corpus Luysii. The pallidum was reconstructed also, but it is practically surrounded by the striatum and can only be seen from the medial view. The lateral part of the thalamus, where it did not overshadow any of the structures we were studying, was also reconstructed, as was the lateral part of the amygdaloid nucleus where it comes into close relation with the tail of the caudate. The rostral fusion of the caudate and putamen can be appreciated in this model, and the cellular bridges along the body and tail of the caudate which join with the putamen. Smaller cell bridges exist between the caudate and the globus pallidus and the close juxtaposition of these two nuclei is appreciated. The relationship between the head of the caudate and the anterior perforated space and the ventral surface of the brain is seen. A confluence exists between the tail of the caudate, the putamen and the amygdaloid. Tentative delimitations have had to be made awaiting silver material and further cell preparations. The reconstruction will serve as a starting point to study myelination and phylogeny.

The Basic Nitrogenous Extractives of Necturus Muscle.—D. WRIGHT WILSON and WILLIAM A. WOLFF (Laboratory of Physiological Chemistry, University of Pennsylvania). The composition of muscle varies considerably among the different orders of animals. Creatin, carnosin, anserin and carnitin are found in the higher vertebrates and arginin and betain are found in the invertebrates. The isolation of extractives from the muscle of Amphibians has never been reported.

An aqueous protein-free extract of *Necturus* skeletal muscle was precipitated with phosphotungstic acid. The filtrate yielded creatin. The precipitate was fractionated with silver nitrate and barium hydroxid. Carnosin was isolated from the third silver precipitate and identified as the free base and as the characteristic copper salt. The fraction not precipitated by silver yielded trimethylamin oxid as a picrate. Betain and anserin were not obtained.

This is the first report of an isolation of trimethylamin oxid from a fresh water animal. It has previously been found in the muscles of salt water fish and in cephalopods but has never been found in fresh water fish. Its presence in the river crab has been suggested by an indirect quantitative study.

The Renal Excretion of Inulin, Creatinin and Xylose in Normal Dogs.—A. N. RICHARDS, B. B. WESTFALL and PHYLLIS A. BOTT (Laboratory of Pharmacology, University of Pennsylvania). The plasma clear-

ances of inulin and creatinin, simultaneously measured in normal dogs, were found to be of the same order of magnitude. The plasma clearance of xylose was found to be significantly less than that of inulin. These results harmonize with the view that in dogs the plasma clearance of creatinin is more nearly a true measure of glomerular filtration than is that of xylose.

The reasons for choosing inulin as the subject of study in these experiments were:

1. Its molecular weight is high and, compared with creatinin or xylose, its diffusibility is low.

2. It is not hydrolyzed in the animal body but, when injected intravenously, is excreted rapidly by the kidney, in high concentration and completely.

3. Its concentration in urine and plasma can be determined quantitatively by measurement of reducing power after hydrolysis by acid.

4. It is filterable through collodion membranes which are impermeable to protein and through the glomerular membranes of amphibia.

5. It is not excreted by the aglomerular kidney of the toadfish.

From these characteristics inulin might be expected to be filtered through the glomerulus, to be neither secreted nor actively reabsorbed by the tubule and to diffuse out of the tubule more slowly than xylose. The results do not disagree with this expectation.

The Renal Excretion of Creatinin and Certain Organic Compounds of Iodin.—E. M. LANDIS, K. A. ELSOM and P. A. BOTT (Laboratory of Pharmacology, University of Pennsylvania, and the Renal Clinic, University Hospital). The plasma clearances of Skiodan (mono-iodo-methane sulphonate of sodium), Neoskiodan or Diodrast (3:5 diiodo-4-pyridon-N-acetic acid diethanolamine) and Hippuran (sodium ortho-iodohippurate) were compared with that of creatinin.

In unanesthetized dogs Skiodan clearances were approximately equal to, or slightly lower than, the simultaneous creatinin clearances, regardless of the level of plasma Skiodan, within the limits studied. Neoskiodan clearances, on the contrary, ranged from 3.85 to 0.96 times the creatinin clearances. Identical with creatinin clearances when plasma Neoskiodan was high, they became several times greater than creatinin clearances as plasma Neoskiodan approached zero. Hippuran clearances ranged from 2.3 to 0.76 times the creatinin clearances and were similarly dependent upon the concentration of Hippuran in plasma, except that they became slightly, but definitely, lower than creatinin clearances when the concentration of plasma Hippuran was high.

In man the dosage of organic iodine was necessarily limited to amounts which could be administered with complete safety; the concentrations of organic iodine in human plasma were therefore much lower than in dog plasma. Human blood plasma was cleared of Skiodan and creatinin at approximately the same rate, the clearance ratios ranging from 1.13 to 0.85 even when the concentration of Skiodan in plasma was very low. The clearances of Neoskiodan and Hippuran, however, ranged from 1.5 to 6.8 times those of creatinin.

Changes in Duodenal Motility Associated with Gastric Peristalsis.—J. E. THOMAS and J. O. CRIDER (Laboratory of Physiology, Jefferson Medical College). A study by graphic methods of gastric and duodenal activity during digestion in unanesthetized dogs confirms the observations of others on anesthetized animals that rhythmic activity in the duodenum is regularly diminished or absent while a gastric peristaltic wave is approaching the pylorus and increased at the end of the antral cycle.

The gastric peristaltic wave may pass over the pylorus to the duodenum but the following new facts do not support this interpretation: (1) The activity of the duodenum at the end of the antral cycle does not conform to the usual description of intestinal peristalsis. (2) Its rate of transmission in the duodenum (10 cm. per second) is too fast for peristalsis but agrees with the rate of conduction of descending inhibition. (3) The gastric influence appears to diminish duodenal activity instead of increasing it.

The authors prefer to attribute the result to inhibition advancing ahead of the antral wave. The activity at the end of the antral cycle may be independent activity characteristic of the uninhibited duodenum.

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